ANESTHESIOLOGY™2014
OCTOBER 11-15 | NEW ORLEANS, LA

Session: L102
Session: L165

Malignant Hyperthermia in a Child Having a Tethered Cord Release

Tae Kim, M.D.
The Johns Hopkins Medical Institution, Baltimore, MD

Disclosures: This presenter has no financial relationships with commercial interests

Stem Case and Key Questions Content

A 5 year old, ASA I, girl weighing 15.7 kg is scheduled for a tethered cord release. Past medical history is significant for asthma, muscle cramps with minimal exertion, especially on hot days, weak legs, and a previous uneventful general anesthetic with an inhalational agent for strabismus surgery. A MRI evaluation for scoliosis demonstrates a tethered cord. The mother states an uncle passing away under unknown circumstances during or shortly after an operation. The mother had a C-section under general anesthesia and her step brother a circumcision under general anesthesia without complications. There is no family history of neuromuscular disorders. Medications include flovent and albuterol inhaler prn. Allergies: NKDA
Are there any concerns about her past medical history or planned procedure? Would you like any additional information or studies? Is there a reliable way to screen for neuromuscular disorders associated with adverse anesthetic events?

Anesthesia is induced with N20, 02, sevoflurane and tracheal intubation facilitated with rocuronium. Intravenous medications include glycopyrrolate, fentanyl, and cefazolin. The patient is positioned prone with her arms and hands up toward you. Auscultation reveals equal and bilateral breath sounds. Volume controlled ventilation starts with a peak inspiratory pressure(PIP) of 18 cmH20 and an end-tidal carbon dioxide (EtC02) of 40 mmHg. The surgeon requests no more muscle relaxant be given after the start of the operation.
What are some complications associated with prone positioning? Do you agree with the anesthetic plan as described?

Surgical dissection reveals a tethered cord. Fifty-five minutes after induction, the EtC02 is noted to be gradually increasing to the mid to upper 50s. Heart rate and blood pressure remain stable with minor variations. Frequent adjustments to minute ventilation have only transitory effect.
What is your differential diagnosis for the difficulty in ventilation? How will you proceed in addressing this problem?

You inform the surgeon you have exhausted all maneuvers to improve ventilation. You would like to administer more muscle relaxant, because you are having difficulty ventilating. The surgeon is not happy, but agrees with your request. Additional doses of fentanyl and rocuronium are administered, but the EtC02 continues to rise with a maximum value of 85 mmHg and a PIP of 43 cmH20. The patient becomes more tachycardic and develops muscle rigidity. Also, the esophageal temperature rises quickly from 36oC to 41°C.

You suspect you may have a case of malignant hyperthermia. What is malignant hyperthermia?

Copyright © 2014 American Society of Anesthesiologists

How is it possible for the patient to develop muscle rigidity after having received a muscle relaxant? Would you redose the muscle relaxant or change to a different type of muscle relaxant? Is this a typical finding for malignant hyperthermia (MH)? Name some other clinical findings indicative of MH. How is MH different from Neuroleptic Malignant Syndrome? What are your immediate concerns in managing a suspected case of malignant hyperthermia?

Three of your colleagues come to your aid, as well as one eager medical student who happens to be on rotation. What is the most effective way to utilize all this help? What is dantrolene and how is it administered? What will you look for to guide your therapy?

As you are preparing to inject the first dose of dantrolene, you notice a short run of ventricular tachycardia on the ECG monitor. The patient remains hemodynamically stable during this period. However, the ventricular tachycardia becomes more frequent and multifocal.
What is your initial assessment and how will you proceed in the treatment of this arrhythmia. Is lidocaine contraindicated? Would you use calcium to treat hyperkalemia? What are some other options in the management of ventricular arrhythmias?

Table 1

Arterial Blood Gas					
	pH	pCO2	pO2	HCO3-	Base Deficit
Pre-dantrolene	6.9	85	135	16	-13
Post-dantrolene	7.14	67	210	21	-8

Looking at table 1, what is your interpretation of the initial arterial blood gas?
The patient receives a second dose of dantrolene. The patient becomes much easier to ventilate and the EtC02 begins to normalize. The heart rhythm returns to normal. Another arterial blood gas demonstrates improvement of the acid-base status. The surgeon notes the overall improvement in the patient and would like to continue the operation. Your last arterial blood gas shows: pH -7.28 pC02 -53 p02 -325 HC03--23 base deficit --4.2.

Would you allow the surgeon to continue? What information will you consider in deciding to continue or halt the operation? Does the type of operation have any influence on your decision? As the case nears the end, the neurosurgeon expresses concern for the child's lower motor function. Therefore, he "prefers" the child awake and extubated for a neurological examination. What are your thoughts?

The PICU staff is informed of the MH episode and given the MH Hotline telephone number. What is the MH Hotline and what is the telephone number?

From talking with the MH Hotline Consultant, it is determined the clinical grading score for this case is 58. What does this number mean? What is the Larach Clinical Grading Scale? Does she need to have a test for MH susceptibility? What kinds of tests are available for MH? Should her family be tested?

The child continues to show evidence of a metabolic acidosis requiring dantrolene for another 48 hours. The child complains of mild nausea and slight weakness during this time.
What are some common side effects associated with dantrolene? If this child were under your care for a muscle biopsy, how would you manage her anesthesia? Would you pretreat her with

Copyright © 2014 American Society of Anesthesiologists

dantrolene? If this child presented for an umbilical hernia repair with the same history and no MRI evaluation, would you treat her differently?

Model Discussion Content

Malignant hyperthermia (MH) is an inherited autosomal dominant disorder with incomplete penetrance. It is described as a hypermetabolic state triggered by exposure to halogenated volatile anesthetic gases and succinylcholine in susceptible individuals. Its reported incidence varies greatly from 1:5000 to 1:65000 anesthetics. However, recent studies based on US hospital data point to an incidence of 10 to 13 patients per million hospital discharges. Overall mortality was 11.7% during hospitalization.

In children, the incidence is reported as 1: 15,000 anesthetics. Half of all MH episodes occur in children less than 15 years old. However, two recent studies looking at US national and state hospital data indicate the actual percentage in children less than 15 years of age to be less. The percentage reported ranged from 17% to 45% below the age of 19 years old. There is regional variability with the most cases reported in Wisconsin, Nebraska, West Virginia and Michigan. Many patients do not realize they are MH susceptible, until a crisis occurs.

The metabolic derangement of malignant hyperthermia focuses on the uncontrolled release of calcium into the myoplasm by the sarcoplasmic reticulum. A genetic defect of the ryanodine receptor (RYR-l) allows for uncontrolled regulation of the calcium channels. This allows for the contraction of skeletal muscles resulting in increased metabolic activity as a result of exposure to halogenated volatile anesthetic gases and succinylcholine. This hypermetabolic state leads to the increased requirements for oxygen for aerobic metabolism. The high demand results in an oxygen deficit requiring the use of the anaerobic pathway to sustain metabolic activity. This causes the metabolic acidosis associated with MH.

The diagnosis of malignant hyperthermia susceptibility may be either by a muscle biopsy or genetic testing. The Caffeine Halothane Contracture Test (CHCT) is the most sensitive test. This is offered in four centers in the United States and two in Canada. It requires exposing a fresh muscle specimen of approximately 2 grams to varying concentrations of caffeine and halothane. The amount of tension generated is compared to known standards. A positive test would show an exaggerated response.

Genetic testing is comparatively insensitive. There are over 30 gene mutations associated with MH and the number continues to grow with more MH reporting and confirmation with muscle testing. A blood sample is required for this test. The DNA is examined for a gene mutation that matches any of the currently known mutations. If there is a match then the person is MH susceptible. However, there is a low sensitivity to the test of 30%. Also, the lack of a match does not ensure not being MH susceptible. There are only two centers in the United States, the Center for Medical Genetics, University of Pittsburgh Medical Center and Prevention Genetics LLC that perform the genetic screening test.

The clinical diagnosis of a malignant hyperthermia episode was aided by the development of a clinical assessment tool by an international panel of MH experts. The Clinical Grading Scale CGS) was developed by Dr. Larach and colleagues to evaluate certain clinical manifestations and laboratory findings associated with MH. It was designed to assess the probability an

Copyright © 2014 American Society of Anesthesiologists

anesthetic event represented a true MH episode and to assist in defining the patient's MH susceptibility with additional testing. However, the scale lacked sensitivity because the observer scoring the event had to make a judgment on whether specific clinical signs were appropriate for the patient's medical condition, anesthetic technique, and surgical procedure. Also, all the components in the CGS could not always be applied to every case.

Preoperative screening for malignant hyperthermia susceptibility should be included in the preoperative evaluation. There may be a family history of anesthetic related deaths, because of its genetic association. However, many patients may have undergone a general anesthetic without difficulty and are unaware they are MH susceptible. It is not uncommon for some patients to have undergone general anesthesia on several occasions without incident. Inquiry should be made into any family history of any adverse reactions to anesthesia, especially unexplained death. Also, questions should be directed to any family history of neuromuscular disease, such as Central Core Disease or King Denborough Syndrome.

The clinical manifestations of malignant hyperthermia may be mimicked by common problems encountered in the operating room. Equipment malfunction, such as a faulty one way valve or exhausted soda lime may result in erroneous end tidal C02 values. Displaced endotracheal tube or mucous plugging may make ventilation difficult. Light anesthesia may result in increased muscle tone and tachycardia. Fever secondary to infection, hyperthyroidism, pheochromocytoma or inadvertent overheating of the patient may be misinterpreted as a sign of MH. Also, drug reactions may cause tachycardia or hyperthermia. Neuroleptic malignant syndrome (NMS) resulting from the use of antipsychotic drugs may mimic MH. Patients may experience muscle rigidity, fever and hemodynamic instability.

Laboratory findings may include an elevated creatine kinase, hyperkalemia and metabolic acidosis. The underlying mechanism is the reduction of dopamine levels or the blockade of dopamine receptors. Treatment is supportive and administration of dopaminergic medications. Dantrolene is able to treat NMS. Serotonin Syndrome is another condition mimicking MH. It results from an increase of serotonin in the central nervous system. Both conditions show no inherent cross susceptibility to MH. Other neuromuscular disorders were once thought to be associated with MH based on their clinical presentation. The dystrophinopathies, such as Duchenne Muscular Dystrophy, have proven to be unrelated to MH. The use of succinylcholine triggered rhabdomyolysis and release of high concentrations of potassium and myoglobin. Also, the defective gene for the disorder is found on the X chromosome.

The diagnosis of a malignant hyperthermia episode in the operative setting often is a clinical diagnosis. The patient may suddenly manifest a rapidly increasing end-tidal C02 that is unresponsive to changes in minute ventilation. This is usually the first sign. Tachycardia and tachypnea, if the child is spontaneously breathing, may soon follow. Trunk or total body rigidity may develop along with hyperthermia as a late sign. These taken together with consideration of the child's underlying medical problem and the stage of the operation may help to reach a diagnosis.

In addition, the onset of malignant hyperthermia in rare instances may occur after the surgery. In one study analyzing cases from the North American MH Registry, it was found that 10 cases of MH occurred in the postoperative period. The times ranged from 0 to 40 minutes after the

Copyright © 2014 American Society of Anesthesiologists

cessation of anesthesia. Unfortunately, there are some patients who succumb early to MH from a lethal arrhythmia secondary to hyperkalemia.

Masseter spasm from succinylcholine use may be a harbinger for MH. There is a 25% incidence of MH with masseter spasm. This event requires the anesthesiologist to make a qualitative assessment as to the degree of severity, the likelihood of MH susceptibility and whether to continue the anesthetic. If limb muscle rigidity is also noted,then dantrolene sodium treatment should commence immediately. Patients experiencing true masseter muscle rigidity should be admitted for observation. Patients should be observed for any signs of MH and changes in urine color. Breakdown of muscle tissue may result in myoglobinuria, causing a cola-colored urine. Also, blood samples should be analyzed for any changes in creatine kinase or serum electrolytes. Creatine kinase levels above 20,000 I.U. are associated with positive muscle biopsies in greater than 80% of patients.

The acute phase of treatment of malignant hyperthermia according to the Malignant Hyperthermia Association of the United States begins immediately with getting help and getting dantrolene sodium. The surgeon should be notified of the presumptive diagnosis and the volatile agents discontinued. The patient does not have to be disconnected from the anesthesia circuit, but the patient should be ventilated with high flow (10 L/min) 100% oxygen and the procedure ideally terminated.

Dantrolene sodium is the drug of choice to treat a MH episode. The drug comes in a 20 mg vial,and needs to be dissolved with 60 ml of sterile preservative-free water for injection. In the pediatric population the weights vary tremendously, and the number of additional personnel to mix the drug also varies. Pre-warming of the water with a temperature not to exceed 38°C helps to solubilize the dantrolene. Also, the dantrolene sodium vials contain NaOH for a pH of 9 and 3 gms of mannitol for isotonicity. Sodium bicarbonate may be administered to empirically to treat metabolic acidosis and then should be given based on arterial blood gas results.

As the name implies, patients become very hot and require the use of active cooling techniques. The patient core temperature may reach >39°C. A core temperature above 42°C is typically associated with multi system organ failure and death. Active cooling techniques may include lavage of open body cavities, stomach, bladder or rectum with cold saline solution. Active cooling should be stopped when the core temperature is 2 ml/kg/hr to avoid myoglobinuria-induced renal failure.

In the post acute phase, it is recommended to admit the patient to the intensive care unit. If the MH episode was aborted early, the patient should stay for at least 24 hours due to the risk of recrudescence. Dantrolene may be continued in the postoperative period at a dose of 1 mg/kg every 4-6 hours or .25 mg/kg/hr by infusion for at least 24 hours. The administration of dantrolene beyond this time may be dictated by a recurrence of acidosis as documented by arterial blood gas. Arterial blood gases are drawn as clinically indicated and creatine kinase (CK)is drawn every 6 hours. The highest level of CK is typically noted on day 2 or 3. Urine output must be followed and maintained. The concern for acute rhabdomyolysis and myoglobinuria may require maintaining a urine output >200 ml/h or 2 ml/kg/hr and alkalinizing the urine with a sodium bicarbonate infusion.

Finally, counseling for MH testing should be offered to the family and the child registered with

Copyright © 2014 American Society of Anesthesiologists

the MH registry. MH Hotline 1-800-MH-HYPER (1-800-644-9737), if outside the U.S. 1-315-464-7079. MH-susceptible patients may be safely anesthetized using non-triggering anesthetic drugs and techniques, which excludes the use of halogenated volatile anesthetic gases for general anesthesia and succinylcholine for muscle relaxation. The use of local anesthetics for regional anesthesia and all other anesthetic medications, excluding those previously cited, are safe for an intravenous technique, such as total intravenous anesthesia. All facilities should have a treatment plan for MH and the necessary equipment and drugs to treat an MH episode. A properly stocked MH cart will have a minimum of 36 vials of dantrolene sodium for injection and sterile preservative free water. Dantrolene prophylaxis is not recommended, because it can worsen muscle weakness in patients with muscle disease.

The preparation of anesthesia machines has become more complex. In the past, it was generally accepted that anesthesia machines should be prepared by removing or disabling the vaporizers. The C02 absorbent should be replaced and the anesthesia circuit flushed with 10 L/min of oxygen for at least 20 minutes. Ten minutes are required using a fresh gas hose. The ventilator may be flushed by connecting a breathing bag during this time. However, the increasing complexity of the internal components of a modern day anesthesia machine or workstation has required more individualized approaches to degassing the machine. There have been numerous articles addressing specific anesthesia machines and how to prepare them, such as the Drager Fabius and Drager Primus. MH susceptible patients for outpatient surgery may be discharged on the same day after an uneventful operation. They should be monitored in the PACU for a total of 2.5 hours, after which if there is no event, they may be discharged home. In summary, malignant hyperthermia is a metabolic disorder that is difficult to detect prior to anesthesia. Patients may experience general anesthesia multiple times before having their first malignant hyperthermia crisis. Screening is difficult, unless there is a known family history of malignant hyperthermia. The Caffeine-Halothane Contracture Test remains the gold standard to identify those individuals at risk for malignant hyperthermia. Genetic testing is available, but the sensitivity is poor. Dantrolene remains the only drug capable of treating a MH episode.

However, the prophylactic use of dantrolene is discouraged due to its many side effects. MH susceptible individuals may safely have anesthesia for surgery with non-triggering medications and anesthetic techniques.

References

1. Bonciu M, de la Chapelle A, Delpech H, et al. Minor increase of endtidal C02 during sevoflurane-induced malignant hyperthermia. Paediatr Anaesth. 2007 Feb;17(2):180-2
2. Brady JE, Sun LS, Rosenberg H, Li G. Prevalence of Malignant Hyperthermia Due to Anesthesia in New York State, 2001-2005. Anesth Analg. 2009 Oct;109(4):1162-6
3. Brandom BW. Malignant Hyperthermia In: Motoyama EK, Davis PJ, eds. Smith's Anesthesia for Infants and Children, 7th edn. Philadelphia: C.V. Mosby, 2006, pp.1015-1031
4. Brandom BW. Genetics of malignant hyperthermia. ScientificWorld Journal. 2006 Dec 28;6:1722-30
5. Burkman, JM, Posner KL, Domino KB. Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. Anesthesiology. 2007 May;106(5):901-6
6. Flick RP, Gleich SJ, Herr MM, Wedel DJ. The risk of malignant hyperthermia in children undergoing muscle biopsy for suspected neuromuscular disorder. Paediatr Anaesth. 2007 Jan;17(1):22-7

Copyright © 2014 American Society of Anesthesiologists

7. Gronert GA, Pessah IN, Muldoon SM, Tautz TJ. Malignant Hyperthermia. In: Fleisher LA,Johns RA, Savarese JJ et al, eds., Miller's Anesthesia, 6th ed. Philadelphia, Pennsylvania,Elsevier Churchill Livingstone, 2005, pp.1169-1190
8. Gunter JB, Ball J. Than-Win S. Preparation of the Drager Fabius anesthesia machine for the malignant-hyperthermia susceptible patient. Anesth Analg 2008 Dec;107(6):1936-45
9. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in north america from 1987 to 2006: a report from the north american malignant hyperthermia registry of the malignant hyperthermia association of the United States. Anesthesiology 2008 Apr; 108(4):603-11
10. Larach MG, Localio AR, Allen GC et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology. 1994 Apr;80(4):771-9
11. Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. JAMA. 2005 Jun 15;293(23):2918-24
12. Litman RS et al. Postoperative Malignant Hyperthermia An Analysis of Cases from the North American Malignant Hyperthermia Registry. Anesthesiology 2008 Nov; 109(5):825-9
13. Malignant Hyperthermia Association of the United States. Emergency Therapy for Malignant Hyperthermia, www.mhaus.org.
14. Parness J, Lerman J, Stough RC. Malignant Hyperthermia. In: Cote CJ, Lerman J, Todres ID,eds. A Practice of Anesthesia For Infants And Children. 4th Ed. Philadelphia:Elsevier Saunders,2009, pp.847-866
15. Petroz GC, Lerman J Preparation of the Siemens KION anesthetic machine for patients susceptible to malignant hyperthermia. Anesthesiology 2002 Apr;96(4):941-6
16. Pollock N, Langton E, Stowell K, et al. Dantrolene--a review of its pharmacology,therapeutic use and new developments. Anaesthesia. 2004 Apr;59(4):364-73
17. Prinzhausen H et al. Preparation of the Drager Primus anesthetic machine for malignant hyperthermia-susceptible patients. Can J Anaesth 2006 Sep;53(9):885-90
18. Rosenberg H, Davis M, James D et al. Malignant Hyperthermia. Orphanet J Rare Dis. 2007 Apr;24:2:21
19. Rosero EB, Adesanya AO, Timaran CH, Joshi GP. Trends and Outcomes of Malignant Hyperthermia in the United States, 2000 to 2005. Anesthesiology 2009 Jan; 110(1):89-94
20. Zanette G, Robb N, Zadra N, et al. Undetected central core disease myopathy in an infant presenting for clubfoot surgery. Paediatr Anaesth. 2007 Apr; 17(4):380-2

Copyright © 2014 American Society of Anesthesiologists