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Temperature Monitoring during Surgical Procedures

Posted in 2012

Recommendation:

MHAUS recommends core temperature monitoring for all patients given general anesthesia lasting more than 30 minutes. Appropriate sites for continuous electronic core temperature monitoring include the esophagus, nasopharynx, tympanic membrane (with probe in contact with the membrane), bladder, and the pulmonary artery.

Background:

Malignant hyperthermia (MH) is an inherited pharmacogenetic syndrome that can be triggered by commonly used volatile anesthetic agents and/or succinylcholine (1,2). The phenotype is highly variable and a patient may receive a triggering agent without consequences and then, on a subsequent exposure, develop a full-blown MH crisis (1).

The prevalence of MH related to exposure to anesthesia has been estimated at 1 per 100,000 surgical inpatient procedures based on New York State hospital discharge data and 0.3 per 100,000 ambulatory surgery procedures based on New York and New Jersey ambulatory surgery data (3,4). Although MH mortality rates are low, they are not zero, and estimated to be 0.0082 per 100,000 United States surgical inpatients — thus constituting 1% of all anesthesia mortality for the years 1999 to 2005 (5). The North American Malignant Hyperthermia Registry of MHAUS has received reports of 12 deaths from MH in the US for the period of 1987 through 2012, 11 of which occurred in patients less than 46 years old. Mortality rates have increased from 1.4% of cases for the period of 1987 to 2006 to 9.5% for the period of 2007 – 2012 (6,7).

In a study of 84 MH patients, there was a significant association between mortality from an MH event and type of temperature monitoring present prior to the first sign of MH. The relative risk of death when temperature was not measured compared to core temperature measurement was 13.8. The relative risk of death when a skin temperature probe was used versus a core temperature probe was 9.7. Peak temperature best distinguished patients who survived from those who died (7). Economic analysis demonstrates that the economic risks of not monitoring with core temperature probes are easily outweighed by the economic benefit in lives saved (8). Failure to detect and treat temperature abnormalities increases the likelihood of MH complications 2.9 times for every 2°C increase in maximum temperature (1).

Interpretation:

Temperature elevation may be the first sign of MH, and can present within 30 minutes of anesthetic induction (1). However, core temperature perturbations during the first 30 minutes of anesthesia are difficult to interpret because of redistribution hypothermia (9). We therefore recommend core temperature monitoring for general anesthetics exceeding 30 minute, a recommendation that strikes a balance between thermoregulatory and MH studies (10).

Level of evidence:

Our recommendation is largely based on Level 3 or 4 evidence following the Oxford Center for Evidence Based Medicine' (www.cebm.net) levels of evidence. The infrequent and unpredictable occurrence of MH combined with the potential morbidity and mortality of an experimentally triggered MH event makes it unlikely that these issues will be able to be studied in a fashion that would produce higher levels of evidence.

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Preparation of Anesthesia Workstations to Anesthetize MH Susceptible Patients

Posted in 2012

Recommendations (4 alternatives):

1. Flush and prepare workstation according to manufacturer's recommendations or published studies; this may take 10 to >90 minutes. Most studies also physically disconnect vaporizers from the workstation; use a new, disposable breathing circuit; and replace the carbon dioxide absorbent. During the case, fresh gas flow should be kept at 10 liters per minute to avoid "rebound phenomenon" (increased release of residual volatile anesthetic agent when fresh gas flow is reduced after a set period of flushing).

OR

2. Use commercially available activatedcharcoal filters that have been shown to remove trace levels of volatile anesthetic agents following a 90 second flush with high fresh gas flows. These filters have been demonstrated in one in vitro study to be effective for 12 hours.

OR

3. If available, use a dedicated "vapor free" machine for MH-susceptible patients. The machine must be regularly maintained and safety-checked.

OR

4. If appropriate to the institution, use an ICU ventilator that has never been exposed to volatile anesthetic agents.

Supporting Evidence:

Search Strategy: We searched Medline (1948 to May 2011) for the keywords "malignant hyperthermia", "anesthesia", and "equipment". We reviewed those abstracts for pertinent articles, and then hand searched those articles' references for additional studies. We also searched the ASA Abstracts website for additional studies from 2006 to 2010. Finally, we reviewed data provided at the Dynasthetics website not found by earlier search (www.dynasthetics.com).

Background:

MH is an inherited pharmacogenetic disorder that is triggered by commonly used volatile anesthetic agents (1). These agents should be avoided when providing general anesthesia to MH-susceptible patients. There is no known upper safe limit of exposure to these agents, and anesthesia workstations are "contaminated" by them, so efforts must be made to reduce patient exposure to a minimum. MH susceptible swine did not develop MH when exposed to halothane 5 ppm concentration (2). This trace level has been used as an arbitrary "safe limit" to study preparation of workstations and the occupational exposure of MH susceptible healthcare workers.

Key Points:

The earliest solution to this problem was the use of a "vapor free" anesthesia circuit, either a dedicated anesthesia machine that had never been exposed to volatile anesthetic agents, or a disposable non-rebreathing circuit. However, maintaining a dedicated machine for the rare MH patient is impractical in most centers, because of cost and obsolescence (lack of familiarity, availability of spare parts).

Various preparation methods and flushing cycles have been used to wash volatile agents out of absorbent parts of the anesthesia machine that cannot be replaced. These machines have evolved into more sophisticated "workstations" that take

longer to flush because more absorbent materials are used in their construction. Different manufacturers' workstations require specific preparation, especially flush times, so a generic set of instructions on preparation cannot be provided (3). A common problem with flushing a contaminated anesthesia workstation is the "rebound phenomenon" (3), where residual anesthetic agents diffuse out of absorbent materials when the fresh gas flow used for flushing is reduced to "usual" clinical settings (e.g., from 10 to 2 liters per minute).

The use of charcoal filters to remove volatile anesthetic agents is not new, but only recently has a commercially available product been tested to determine how quickly it could achieve a result equivalent to established preparation and flushing methods. In an anesthesia workstation saturated with volatile anesthetic agent, the Vapor Clean™ charcoal filter system reduced trace volatile anesthetic concentrations to < 5 ppm in < 2 minutes, and kept them < 5 ppm for 12 hours.[1,2]

1. Bilmen JG, Gillies RL. Clarifying the role of activated charcoal filters in preparing an anaesthetic workstation fro malignant hyperthermia-susceptible patients. Anaesth Intensive Care 2014; 42: 51-58 [Note: This study used one filter instead of two which is off-label use and NOT recommended]

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Author Commentary:

This is Level 5 evidence (bench research, expert opinion) following the Oxford Centre for Evidence Based Medicine's (www.cebm.net) levels of evidence.

The threshold of 5 ppm is based on a 1996 study of MH susceptible swine (2), the most common in vivo model for human MH. However, this abstract was never published in full and the study has not been replicated. The upper safe limit of trace anesthetic agents in MH susceptible humans is actually unknown. Some cited bench studies measured in vitro trace gas levels using the Miran? gas analyzer, which was designed for measurement of ambient air, not closed circuit bench experiments (4,6). Significant differences among brands and models of workstations mean that each model must be specifically prepared; adequate preparation is hypothetical for any workstation not reported in the literature or by its manufacturer.

Discontinuing the triggering anesthetic agent and increasing fresh gas flow with 100% oxygen is part of the treatment algorithm for MH (7). This recommendation is based on expert opinion, but anecdotally there are MH cases that resolved with only these measures. No study answers the question if the above mentioned machine alterations, or the addition of charcoal filters, would improve patient outcome during an acute MH episode. This question could be answered using the swine model of MH, but the result is unlikely to change current clinical practice.

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Parturient with MHS Partner

Suggested Guidelines for management of the Pregnant-patient not believed to be at risk for MH, but WHOSE PARTNER is susceptible to malignant hyperthermia.

Posted in 2012

The question of the best anesthetic management for labor and delivery of a parturient who is not MH susceptible but whose partner is believed to be MH susceptible is largely theoretic since there are no human or animal clinical studies related to this situation. There are also no cases reported of a fetus of such parents developing a peripartum MH crisis. Nevertheless, since this situation does occur with some frequency, the following are suggested guidelines for anesthetic management.

PRIOR TO DELIVERY:

If at all possible, the father's MH susceptibility should be confirmed by review of medical records. If a genetic test has been done and a known causative mutation found, that mutation can be sought in the fetus prior to delivery (chorionic villus sampling or amniocentesis). However, this course is not recommended by most MH experts at the present time unless the procedures are being undertaken for other reasons. Consultation with the local anesthesiologist and an MH expert, e.g., MH biopsy center director, MH hotline consultant or member of the MHAUS Professional Advisory Council is recommended prior to delivery.

Anesthetic management of a non-MH susceptible woman carrying a potential MH-susceptible FETUS FOR surgery during pregnancy:

If the pregnant woman requires non-emergent surgery at any point in the pregnancy, a non-triggering anesthetic should be employed, such as local, nerve block or epidural or spinal anesthesia as long as it is accomplished in a timely manner. If a general anesthetic is indicated, a total intravenous anesthetic is recommended, although nitrous oxide may be used with an anesthesia machine that has been prepared for an MH susceptible patient. Standard ASA mandated monitoring should be used, along with core temperature monitoring. Fetal monitoring should follow standard guidelines. Dantrolene should not be administered in preparation for surgery, labor and delivery.

LABOR AND DELIVERY:

The labor and delivery should be conducted at a site that follows the American Society of Anesthesiologist's Practice Guidelines for Obstetric Anesthesia.

The anesthesia providers should be notified of the arrival of the patient on the Labor and Delivery Unit as soon as she is admitted.

Until the delivery of the fetus, the mother should be treated as MHS, thus avoiding MH triggering agents. All other drugs and techniques may be used as in any pregnant patient with no special modification based on MH status.

Continuous epidural analgesia is highly recommended for labor and delivery.

If a Cesarean delivery is indicated in a patient who does not have an epidural catheter in place, neuraxial (spinal, epidural, or combined spinal-epidural) anesthesia is recommended, if not otherwise contraindicated.

If a general anesthetic is indicated, a non-triggering anesthetic technique should be employed, e.g., TIVA, although nitrous oxide may be used with an anesthesia machine that has been prepared for an MH susceptible patient.

If a rapid sequence induction is needed, succinylcholine, although a known MH trigger, may be administered* since so little of the drug crosses the placental barrier. However, an appropriate intubating dose of rocuronium for rapid sequence induction may be used in place of succinylcholine. An awake intubation is also an option. After delivery, volatile anesthetic agents may be administered to the mother. If uterine relaxation is necessary prior to delivery, nitroglycerine, 250 µg IV may be used, or NTG sublingual spray, one puff. The dose may be repeated. Another alternative is terbutaline 2.5 mg SQ.

POST DELIVERY:

Following delivery, an umbilical blood sample may be obtained for genetic analysis for MH susceptibility in those cases where the father has been shown to harbor a known MH causative mutation. In this case, the DNA diagnostic center should be contacted prior to obtaining the blood sample.

If the father is not known to harbor a known mutation, the determination of whether to obtain a blood sample for genetic analysis is complex and requires consultation with an MH hotline consultant or member of the MHAUS Professional Advisory Council.

In the absence of any medical problems, the mother and baby should be treated no differently than normal.

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- A few MH experts do not recommend use of succinylcholine in this circumstance.

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MH-Susceptibility and Operating Room Personnel: Defining the Risks

Posted in 2012

Topic

The contraindications for the administration of succinylcholine and the potent volatile inhalational anesthetics to Malignant Hyperthermia Susceptible (MHS) individuals are well documented and defined. However, there are no published data on risks to these individuals associated with environmental exposure to waste gases in the operating room.

In recent years, the question has been raised whether or not MHS individuals or their relatives are at greater risk than the general population to operating room environmental exposures. Since there are no clinical trials that have addressed this question, nor is it likely that such protocol would receive IRB approval, the Malignant Hyperthermia Association of the United States (MHAUS) convened a group of experts to develop a Consensus Statement to guide clinicians in providing recommendations to MHS families.

Background:

MH is a life-threatening pharmacogenetic disorder triggered by the administration of commonly used volatile anesthetics (halothane, enflurane, isoflurane, desflurane, and sevoflurane), the depolarizing muscle relaxant succinylcholine, or both (1). Clinical presentation of the disorder is highly variable, but there is strong evidence that fulminant MH episodes result from a rapid sustained rise in myoplasmic calcium caused by fundamental defect in the ability of muscle to regulate calcium (2). A fulminant MH episode consists of a hypermetabolic crisis manifesting as metabolic and respiratory acidosis, tachycardia, cardiac arrhythmias, skeletal muscle rigidity, and rhabdomyolysis. The incidence of anesthetic-related episodes of MH is between 1 in 15,000 in children and 1 in 50,000 in adults (3). Suspicion of MHS is based on family history of the disorder, or on a history of adverse clinical events during anesthesia suggestive of the syndrome. Since most often MHS is inherited as a dominant trait, when MH is diagnosed in one family member, all first-degree relatives are treated as MHS, despite there being only a 50% probability of transmission of a mutant gene in each individual case. To diagnose an individual's risk of MHS, the in vitro contracture test (CHCT) and the caffeine-halothane contracture test (CHCT) have been developed and standardized by European and North American MU study groups, respectively (4, 5). Significant progress has been made in the last decade in developing a genetic test as an alternative to the invasive muscle biopsy required to perform the IVCT or CHCT (6). While the gene responsible for MH susceptibility in ~50-70% of families is known to be that of the skeletal muscle ryanodine receptor, the calcium release channel in sarcoplasmic reticulum responsible for calcium release during excitation-contraction coupling, the genes responsible for susceptibility in the other 30-50% of MHS families remain elusive at the present time As such, the IVCT or CHCT remain the gold-standard tests for determining MH-susceptibility.

Waste gas exposure in the operating room

While there is a single report of a suspected episode of MH in a nurse attempting to clean up an isoflurane spill, (7) confirmation by muscle biopsy was never performed, and the level of exposure most likely exceeded that which is commonly experienced in hospital operating rooms (OR). The National Institute for Occupational Safety and Health (NIOSH) standard for acceptable OR levels of halothane is 2 parts per million (ppm), which is equivalent to 0.0002%. An abstract published by Maccani reported that MH susceptible swine (a species exquisitely more sensitive than human) did not trigger after exposure to 5 ppm halothane (8). Therefore, in the modern OR with high air turnover, low level exposure is unlikely to trigger MH. There are multiple anecdotal reports of MHS individuals, including anesthesia providers, who have worked and thrived for many years in the OR without adverse incidence (9). Conversely, there are no reports of MH episodes in hospital ORs as a consequence of inhaling waste gases.

Environmental gas exposure outside of the operating room

There are reports of MH-like episodes in biopsy proven individuals from environmental exposures outside of the OR due to the inhalation of halogenated gases from fire extinguishers (10) and gasoline vapors (11). It is not recommended that anyone inhale

noxious vapors in a closed, poorly ventilated space, especially MHS individuals. MHS laboratory personnel working with vapors should perform such work under a hood. MHS veterinary personnel anesthetizing animals should adhere to the same NIOSH requirements for human hospitals, and avoid prolonged exposure to poorly scavenged mask breathing devices.

Summary:

There is no evidence to support restricting the professional choices of MHS individuals; however, caution should be exercised regarding the inhalation of any noxious vapor in a poorly ventilated area.

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Does Mitochondrial Myopathy (MM) Increase an Individual's Susceptibility to Malignant Hyperthermia (MH)?

Posted in 2012

Recommendations

- Review of literature does not indicate an increased susceptibility to MH by patients diagnosed with Mitochondrial Myopathy (MM).
- patients suffering from MM should receive an anesthetic appropriate for the patient's symptoms and the treatment they are receiving as well as the type of surgery they are undergoing
- Volatile agents should not be avoided out of concern for possible MH susceptibility in MM patients.
- Use caution when using succinylcholine in myopathic patients due to evidence suggestive of succinylcholine-induced hyperkalemia in such patients.

Supporting Evidence

Literature Review: Multiple literature searches of the National Library of Medicine, beginning the year 1970, were done using key words: Malignant Hyperthermia; Mitochondrial Myopathy and Cytopathy; Mitochondrial Syndromes; Anesthetic Management; Pediatrics and Perioperative Complications. Individual database searches were performed as well as searches within the major anesthesiology journals (Anesthesiology and Anesthesia & Analgesia) beginning the year 1970. All articles that described anesthetic management of patients with mitochondrial disorders and articles that conducted original research examining the role of mitochondria in relationship to MH were reviewed.

Background:

It is unclear how the attribute of MH first came about in association with MM. The phenotypical presentations of patients with MM involve acidosis that is of a chronic nature and hypotonia of varying severity. Myopathic illnesses that carry known risk for MH such as central core disease (CCD) share similar clinical features and hence an association may have been first considered. The majority of available literature suggests no or weak association between MM and MH.

Evidence Thus Far:

Ohtani et al (1985) in a letter to the editor reported a successfully treated case of MH in a 2 year old diagnosed with MM. The child had clinically evident motor weakness; elevated CK and pyruvate levels, but received halothane and succinylcholine for an unknown procedure. Generalized muscle rigidity, hyperkalemia and rise in temperature to 380 C followed the induction of anesthesia. 50 mg dantrolene (patient's weight unknown, but presumably a large dose for a 2 year old myopathic child) an unknown amount of bicarb and cooling were the treatment instituted. The child recovered in 30 minutes and underwent a muscle biopsy performed with local anesthesia the same day, the analysis of which suggested defective oxidative phoshorylation of the mitochondria.

This brief case report describes a clinical situation where MH is diagnosed in a myopathic child after administering succinylcholine and halothane. All the symptoms and signs except for the temperature of 380C could be due to cytoskeletal disruption of muscle from succinylcholine (Theroux, 2001; Van der Spek, 1987) especially in a child with evidence of ongoing muscle cell damage (elevated CK preoperatively). This case at best provides weak evidence of an association between MM and MH. Nevertheless this letter to the editor has been consistently cited and referenced by numerous other authors as evidence for their statement of MH susceptibility of patients with MM.

Thompson et al (1997) reported the anesthetic course of a 20 year old man with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes) syndrome. The patient had difficulty with anesthesia at a different hospital (other than the author's), and the report clearly notes that MH was excluded in that particular event. However, the authors chose a non-triggering anesthesia citing Ohtani et al (1985). **Non-triggering anesthetics limit the choices of anesthetics available to the anesthesia practitioners and might in fact lead to less desirable choice of anesthetics as in 'choice of propofol based anesthetics for MM'. Note that majority of non-triggering anesthesia includes Propofol which is known to further impair mitochondria.**

Wiesel et al (1991) describes the anesthetic for a 13 month old boy for skin and muscle biopsy. MH triggering agents were avoided, citing Ohtani et al (1985). One sees a pattern emerging where a single case report, has a snow balling effect going forward.

Maslow and Lisbon (1993) report a 40 year old man with MM who was given a spinal anesthetic for reduction of an ankle fracture. One of the reasons stated for performing spinal anesthetic was to avoid triggering anesthesia. Authors mention that there is no evidence to believe that MM renders MH susceptibility but they wished to avoid triggering agents citing Ohtani et al (1985).

Casta et al (1997) describe the perioperative course of a 13 month old who had rapid deterioration of CNS function with MRI findings in the immediate post operative period following general anesthesia for gangrenous gall bladder surgery. Anesthetics consisted of thiopental, isoflurane and nitrous. She developed generalized posturing in the postoperative period indicative of significant CNS dysfunction. It was postulated that this child's worsening condition was due to her defect in oxidative phosphorylation further exacerbated by inhibition of complex III of the electron transport chain by circulating cytokines especially TNF. There was no suspicion of MH as a causative factor. Post operative CNS dysfunction is likely in MM and pathophysiology is directly attributable to the patient's primary pathology of dysfunctional mitochondria. This case report describes the effect of stress induced by anesthesia and surgery on a defective mitochondrial energy resource thus resulting in adverse outcome; there is no relation to MH.

Gronert et al (1979), in an animal study using susceptible swine, concluded 'that the reduced respiratory and calcium binding activities in mitochondria from susceptible swine supported the diagnosis of a myopathy, but that these do not account for the functional and biochemical derangement observed in clinical malignant hyperthermia'. Findings in this study do not support a link between biochemical abnormalities described in MH and those found in the swine in their experiment.

Driessen et al (2007) describe 122 patients with MM who received a variety of anesthetic agents. Only 15 patients were anesthetized using 'total intravenous anesthesia' and the rest received potent Inhalational anesthetics. There were no significant adverse effects related to the choice of anesthetics. This is an important study as the discussion about anesthetic agents revolves around 'to use or not to use volatile anesthetics.' This study supports use of volatile anesthetic agents.

Muravchick et al (2006), in an extensive review of MM state, "Only the very rare mitochondrial myopathies with multicore or minicore histology seem to warrant concerns of an increased risk of MH. Therefore, at least at the present time, there is inadequate data to support the recommendation of some authors that the anesthetic plan for patients with mitochondrial disease should routinely include MH precautions."

Cheam et al (1998) reported the use of a non triggering anesthetic to anesthetize a known case of MM in a child from the Chinese University of Hong Kong. The authors refer to several articles only remotely related or associated with MH.

Fricker et al (1997) describe a 41 year old man with severe exercise intolerance and myalgia with CK 3,700 admitted for MH work up prior to hernia repair. He carried a combined diagnosis of MM and Myoadenylate Deaminase deficiency. [These authors also cite 'Ohtani et al (1985)]. An IVCT test with caffeine and halothane (contracture at 1.5 mm caffeine: 4.5 mN and at 0.11 mm halothane: 2.5 mN, respectively) established the diagnosis MHS (contracture thresholds: more than 2 mN at ? 2 mm caffeine and ?0.44 mm halothane). This study describes a situation where an IVCT performed is positive for MH in an individual

with two myopathic conditions. While it proves that this particular patient may be MH susceptible it cannot be extrapolated to mean an increased susceptibility of patients with MM to MH. It must be remembered that results of contracture testing is difficult to interpret when the patient has a co-existing muscle disease especially in the absence of a clinical presentation.

With regard to the use of succinylcholine in MM patients, although the literature does not support an outright statement regarding use of succinylcholine leading to hyperkalemia in MM, there are reports (Al-Takrouri et al., 2004, Larach et al., 1997) which indicate fatalities from succinylcholine-induced hyperkalemia and rhabdomyolysis in patients with undiagnosed myopathies. Therefore, caution must be utilized when using succinylcholine in myopathic patients due to evidence suggestive of succinylcholine- induced hyperkalemia. Though not directly related to MH, due to the profound and often irreversible adverse effects from succinylcholine in some myopathic patients, a cautionary statement is warranted in the recommendations.

Author Commentary

Mitochondrial diseases are a group of myopathic conditions encompassing a broad spectrum of defects in mitochondria, the clinical features of which can be worsened by illness or stress. Any surgical intervention would mean a finite amount of stress on an individual and in a mitochondrial myopathic patient this stress itself could worsen their clinical status. No controlled clinical trials have been conducted in patients with mitochondrial myopathy to study the effects of anesthetic agents. As such available clinical evidence of Malignant Hyperthermia Susceptibility (MHS) in mitochondrial myopathy predominantly consists of level 4 evidence (case reports, retrospective reviews of patient's anesthetics and expert opinion). One could speculate on a scenario which if MH occurs in a mitochondrial myopathic patient the burden on the already defective mitochondria might result in a clinical presentation which may be completely unrecognizable.

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Adverse Effects of Heat and Exercise in Relation to MH Susceptibility

Posted in 2012

Recommendations

1. Any MHS (MH-susceptible) patient who experiences sudden collapse in association with muscle rigidity and hyperthermia should be immediately treated for MH. This includes immediate cooling measures, and transport to the nearest medical facility in order to treat with the drug dantrolene. Succinylcholine should be avoided during resuscitation and management.

2. MHS patients or their relatives who have not experienced adverse effects of heat and exercise should not restrict their activity. They should carry identification of their susceptibility and inform those responsible for their care of their MH status.

3. MHS patients who have experienced adverse effects of heat or exercise should restrict their activity based on their own experience.

4. Patients who develop documented recurrent rhabdomyolysis after exercise or with heat stroke should be referred to a neuromuscular specialist for evaluation. Malignant Hyperthermia Susceptibility should be considered as part of the evaluation.

Literature review:

All articles that discussed the association of heat/exercise and MH as identified in a literature search through PubMed were reviewed.

Background:

Although it is clear that some patients who experience heat and exercise related rhabdomyolysis and/or outright heat stroke are MH susceptible (MHS), it is not possible at present to prospectively identify those MH susceptibles who will develop signs of MH with exercise and/or heat exposure. A direct causal relationship has not been proven between adverse effects in MHS patients and exposure to heat and exercise, but there is supporting evidence to support an association.

Supporting Evidence:

Significant evidence exists that swine carrying (skeletal muscle ryanodine receptor gene) RYR1 mutations that are causal for MH develop signs of MH upon exposure to heat and with exercise or stress (Aberle et al, 1974). Similarly, genetically engineered mice that display one or more RYR1 mutations will develop signs of MH with heat exposure (Durham et al, 2008).

The evidence for the deleterious effects of heat and/or exercise in humans is based on multiple individual cases reports. In many cases, particularly prior to 2000, supporting evidence derives from muscle contracture testing (IVCT or CHCT) or where the patient derived from a family with MH (Ryan and Tedeschi, 1997).

For example, a French study of 45 subjects with exertional heat stroke evaluated MH susceptibility and other adverse effects in these subjects, using IVCTs performed at least 3 months after the exertional heat stroke episode (Figarella-Branger et al., 1993). This study revealed 11 MHS, 8MHE subjects and 26 MHN. In both groups, whatever the IVCT results, pathological findings were heterogeneous and revealed various changes: rhabdomyolysis, mitochondrial myopathy, denervation, type II atrophy, AMPase deficiency, non-specific findings or normal features.

In 2001, Tobin and colleagues reported a 12 -year old patient with a clinical history of MH who developed signs of MH after soccer practice and died shortly thereafter. He and his family were found to have an MH-related RYR1 mutation (Tobin et al., 2001).

Wappler and colleagues (2001) described 12 healthy young men who developed exercise-induced rhabdomyolysis. Ten were MH positive on contracture test and three manifested RYR1 mutations.

Muldoon's group reported (in an abstract) studies of 15 men who developed exercise- induced rhabdomyolysis, 6 had positive CHCT and three displayed RYR1 causal mutations (Capacchione et al., 2009).

Davis et al (2002) reported on two patients with exercise- induced rhabdomyolysis who also displayed a positive contracture test and RYR1 mutations suspected to be causal. Both patients came from families with MH susceptibility in other members.

Groom et al (2011) reported on two cases of 'awake' MH. In one case a nine year old male patient experienced anesthesia induced MH related to ptosis surgery and then experienced multiple episodes of high fever and rigidity possibly related to environmental factors. The child died following one of the episodes at age nine. The other case was a six year old girl who died suddenly after experiencing high body temperature and rigidity. A previous episode had been corrected with cooling only. The mutation in the RYR1 gene, although novel, effected intracellular calcium flux similar to causal mutations.

Capacchione et al (2011) reported on a six year old boy who developed high body temperature and muscle rigidity after playing in a splash pool. He and his father had marked hyperlordosis. The father's muscle biopsy was positive for MH and displayed changes of CCD. A novel RYR1 variant was detected in the propositus and the father and a sibling with hyperlordosis. The variant was different from the ones reported by Groom et al (2011) for the nine year old boy and the six year old girl and by Tobin et al (2001) for the 12 year old boy.

Capacchione and colleagues (2010) also reported on a 30 year old patient with exercise induced rhabdomyolysis, positive CHCT and mutations in the RYR1 gene, the DHPR (dihydropyridine receptor) gene and the calsequestrin1 (CSQ1) gene. The RYR1 variant was in a different locus from the previous cases mentioned above.

One study of five MH susceptible and five non-susceptibles in an exercise laboratory at room temperature, showed that with vigorous exercise MH subjects developed higher core temperature than non MH subjects (Campbell et al., 1983). In the early stages of exercise a higher lactate level was noted in the MH subjects. However, there were no other signs of MH.

There has not been a large scale prospective study of MH susceptibility either by contracture testing or genetic testing of patients with either heat stroke or heat related problems with or without exercise induced rhabdomyolysis.

Finally, the importance of body temperature in the triggering of MH was demonstrated most clearly in studies of MHS swine who did not develop MH when hypothermic despite anesthesia with MH trigger agents, but did when body temperature was raised to normal levels (Iaizzo, 1996).

Author Commentary

The evidence supporting a relationship between heat, exercise and MH susceptibility is mostly level 4 as per AHRQ criteria, i.e., observational studies and expert opinion. Nevertheless in my opinion, there is a convincing case for associating problems related to heat and exercise with MH susceptibility because high quality data supporting this contention has been derived from genetically engineered animal models of MH as well as from calcium flux changes in response to SR (sarcoplasmic reticulum) calcium releasing agents in cells transfected with mutations from patients who experienced awake MH.

Hence it is prudent to follow the recommendations described above with emphasis on the importance of cooling during such an episode.

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Does Noonan Syndrome Increase Malignant Hyperthermia Susceptibility?

Posted in 2012

Recommendations

- Review of the medical literature does not support a correlation between Noonan syndrome and malignant hyperthermia (MH) susceptibility.
- There are no known contraindications to the use of volatile anesthetics and/or triggering agents in Noonan syndrome patients.

Supporting Evidence

Literature Review:

Searches of the National Library of Medicine were completed using keywords: “malignant hyperthermia”, “Noonan syndrome”, “pediatric anesthesia complications”, “King-Denborough syndrome”. All articles pertaining to anesthetic management and perioperative complications in patients with Noonan syndrome were reviewed. Articles that delineated between Noonan syndrome and King-Denborough syndrome were also reviewed.

Background:

Noonan syndrome is often described as a “Male Turner syndrome” presenting with pterygium colli, short stature, pectus excavatum, webbed neck, down-slanting palpebral fissures and eyelid ptosis, and congenital heart disease (most commonly, pulmonary artery valvular stenosis). King-Denborough syndrome presents with a very similar phenotypic appearance and has a known link to MH susceptibility. There is a commonly held belief that patients with Noonan syndrome also have increased susceptibility to MH (Benca and Hogan, 2009).

Evidence Thus Far:

Hunter et al. (1975) reported an evaluation of the association between MH and Noonan syndrome using creatine phosphokinase (CPK) levels. King and Denborough (1972) had previously described a subgroup of King-Denborough syndrome patients with elevated CPK levels. Hunter et al. described an 11 year old boy with Noonan syndrome and consistently elevated serum CPK levels. This patient underwent 4 uneventful surgical procedures with a total of 190 minutes exposure to halothane and 1 exposure to succinylcholine. Even with the use of these triggering agents, there was no MH in this child.

Lee et al. (2001) reported a case series of 60 Noonan syndrome patients who underwent surgery to fix spinal deformities. The author describes one case of MH in the 60 patients included in the study. In this report, the diagnostic criteria for Noonan syndrome were not described, nor were any details about the purported MH event. One of the coauthors wrote in a letter to the Lancet (Pinsky, 1972) that “it can be argued that most patients with the syndrome are not at risk.”

Author Commentary:

The “evidence” supporting increased susceptibility to MH in patients with Noonan syndrome is extremely weak. We believe there is only one purported case (Lee, 2001), for which the details are unknown. Since the physical characteristics of Noonan syndrome are similar to King-Denborough syndrome (known to be at increased risk of MH susceptibility), we believe that it is possible that a King-Denborough syndrome child could be mislabeled as Noonan syndrome. This assumption preceded the identification of the genetic basis of these disorders. King-Denborough syndrome has been linked to a mutation on chromosome

19 located near the gene that encodes the ryanodine receptor whereas Noonan syndrome is associated with a mutation on chromosome 12.

We recently reviewed the anesthetic records (at the Children's Hospital of Philadelphia) of patients with Noonan syndrome that received triggering anesthetic agents. In 34 patients, there were no incidents of MH in 113 anesthetics. Taking this evidence into account, along with the absence of proof of a Noonan syndrome -MH link in the literature, we conclude that there is no need for MH precautions in Noonan syndrome patients.

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Dantrolene Administration After an MH Event

Posted in 2017

Topic

Following treatment of acute MH, how much dantrolene should be administered and for how long? What criteria should be used to determine stopping treatment with dantrolene?

Recommendations

- After initial bolus dosing to treat the acute MH crisis, maintenance dantrolene should be continued 1 mg/kg/dose every 4-6 hours while monitoring the patient for signs of recrudescence. The hotline consultants agreed that no evidence exists to refute or change the current guidelines that continue this maintenance regimen until the above criteria are met. Current evidence does not suggest that administering the maintenance dose as a bolus or infusion is superior. Bolus administration may serve to remind clinicians to evaluate the patient at regular intervals. The package insert for dantrolene indicates that it should be used within 6 hours of reconstitution; bolus dosing may make compliance with this directive easier.

Supporting Evidence

Background:

Following initial successful treatment of acute MH, MHAUS currently recommends continuing dantrolene therapy for at least 24 hours and sometimes longer as clinically indicated. We recommend that dantrolene can be stopped, or the interval between doses increased to every 8 hours or every 12 hours if all of the following criteria are met: metabolic stability for 24 hours, core temperature less than 38°C, CK continues to decrease, no evidence of ongoing myoglobinuria, and muscle rigidity has abated. The hotline consultants discussed these criteria and searched for evidence that they should change or remain the same.

Discussion:

The most pertinent published data in this area are concerned with the possibility of recrudescence – the recurrence of MH signs after successful initial treatment of the acute event.[1]Recrudescence of MH occurred in 20% of 308 patients examined. Half of the patients showed signs or symptoms of recrudescence within 9 h of the initial event (median time 8.7 h), and 80% did so within 16 h. Signs included muscle rigidity, evidence of increasing rhabdomyolysis, respiratory acidosis, and hyperthermia.

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Relationship Between MH Susceptibility and Heat or Exercise Related Rhabdomyolysis

Posted in 2017

Topic

What is the relationship between malignant hyperthermia susceptibility and heat or exercise related rhabdomyolysis?

Supporting Evidence

Background:

There is a poorly-defined relationship between MH susceptibility and the development of a non-anesthetic MH-like illness during conditions of heat, exercise, stress, or viral illness.[1,2] This non-anesthetic-induced MH-like condition may demonstrate many of the same clinical signs as anesthetic-induced MH including hyperthermia, muscle rigidity, rhabdomyolysis, and life-threatening hyperkalemia. Animal and anecdotal human data suggest that dantrolene is effective in ameliorating consequences of heat stroke.

Many questions remain. In the absence of previous diagnostic testing, when should patients with a history of a non-anesthetic MH-like syndrome related to external conditions be considered to be at special risk for MH when they present for general anesthesia? When should these patients be referred for diagnostic testing for MH susceptibility? Are patients with a suspected or proven susceptibility to MH at greater than normal risk of developing a non-anesthetic MH-like syndrome during non-extreme levels of exercise or heat exposure? If so, should their lifestyles be altered to avoid those conditions? Should competitive athletics be avoided?

Discussion:

The relationship between MH and non-anesthetic MH-like illnesses has been confirmed by experimental human[4] and animal[5] studies as well as human case reports and series.[6] Multiple case reports exist of patients with a history of heat- or exercise-induced rhabdomyolysis who either subsequently developed MH during exposure to anesthetic triggering agents or tested positive when an MH diagnostic muscle biopsy was performed (CHCT or IVCT) or exhibited a pathogenic mutation in the main gene, the RYR1 gene, that is causal for Malignant Hyperthermia.[6-12] These non-anesthetic episodes of rhabdomyolysis have ranged from mild symptoms such as persistent cramping during exposure to heat or exercise,[13] to severe muscle breakdown that resulted in clinically significant rhabdomyolysis,[14] or death due to hyperkalemia.[15]

Conversely, several case reports exist of patients known to be MH susceptible who subsequently developed a serious or fatal MH-like syndrome during exposure to heat or as a result of intense exercise, or both.[16-20] It has been estimated that MH-related *RYR1* pathogenic variants are found in 20 and 30% of cases of heat-or exercise-induced rhabdomyolysis.[21]

Conclusions:

After review of the literature and extensive debate, the hotline consultants were unable to definitively answer the question of whether the patients who have experienced heat or exercise related illnesses should be anesthetized with MH susceptibility precautions. Therefore, the consultants agree that surgical patients with a previous history of a non-anesthesia-related MH-like illness should be considered on a case-by-case basis.

Due to the complex nature of non-anesthesia related MH-like illness, there may be occasions when an anesthesiologist might wish to have the patient evaluated by an expert in neuromuscular disorders to rule out non-MH related etiologies. Evaluation might include endocrine-, inflammatory-, and medication-related myopathies, illicit drug use, muscular dystrophies, and muscle channelopathies (e.g. myotonias). Screening might also include metabolic disorders causing exercise intolerance.

The MH hotline consultants agreed that certain factors related to the clinical characteristics of the MH-like illness may place the patient at a higher-than-normal risk for MH susceptibility. These include (a) delayed return to baseline muscle function (more than a week) after physical exercise; (b) persistent creatine kinase (CK) elevation above five times the upper limit of the laboratory normal range despite rest for at least 2 weeks; (c) rhabdomyolysis complicated by acute kidney injury that does not return to baseline within two weeks; (d) personal or family history of rhabdomyolysis; (e) personal or family history of recurrent muscle cramps or severe muscle pain that interferes with activities of daily living; (f) personal or family history of rhabdomyolysis in response to statin administration; (g) and CK peak > 100,000 U/L.[22]

However, if many other people suffered exercise-related heat stroke or rhabdomyolysis at the same time as the individual or family member, the hotline consultants felt that the event would be less suspicious for an underlying MH susceptibility. Examples would include marathons or football team drills that were conducted despite hot and/or humid conditions.

The hotline consultants also agreed that there is insufficient evidence to determine the estimated risk of non-anesthetic MH-like illness in patients with suspected or confirmed MH susceptibility and thus requires a confident risk-benefit analysis which is currently not possible. It was agreed that as providers, we must communicate with families, coaches, athletic trainers, and the patient's physicians to ensure that signs and symptoms of an MH-like event are quickly recognized and treatment is rapidly instituted. The consultants agreed that MH-susceptible patients who have not experienced adverse effects of heat and exercise should not restrict their activity, and may participate in competitive athletics. However, consultants advise patients to carry identification of their susceptibility and inform those responsible for their care of their MH status. MH susceptible patients who have experienced adverse effects of heat or exercise should restrict their activity based on their own experience and consult with an MH expert, expert neurologist or sports medicine physician familiar with both MH and the adverse effects of heat and exercise. Relatives of MHS patients should be informed and remain aware of their family history of MH. At the present state of the art, deciding which relatives are at risk is a matter of clinical judgement and will remain so until reliable, non-invasive tests are widely available.

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How Much Dantrolene Should be Available in Facilities Where Volatile Agents are not Available or Administered, and Succinylcholine is Only Stocked on Site for Emergency Purposes?

Posted in 2018

Supporting Evidence

Background:

Most MH cases are triggered by the administration of a volatile anesthetic agent with or without succinylcholine, but in a small percentage of cases MH appears to be triggered by succinylcholine alone in the absence of a volatile agent.[1,2] For example, 1.4% of "very likely" or "almost certain" (terms derived from the MH clinical grading scale[3]) MH events reported to the North American Malignant Hyperthermia Registry (NAMHR) were triggered by succinylcholine alone (personal communication, Michael Young, M.S., NAMHR, February 9, 2017).[1,4] In a report from the University of Toronto MH testing center, 20 of 129 (15.5%) biopsy-proven MH events were triggered by succinylcholine alone.[2] In Europe, 2 of 200 (1%) biopsy proven MH events were due to succinylcholine alone.[5] As a patient safety and advocacy organization, MHAUS has recommended[1] "*Dantrolene must be available for all anesthetizing locations where MH trigger agents are used.*" Furthermore, MHAUS recommends that centers stock a minimum of 36 20-mg vials of Dantrium or Revonto (total dose 720-mg), or three 250-mg vials of Ryanodex (total dose 750-mg). These amounts of dantrolene were originally determined by the analysis of MH event data showing that some cases of acute MH required up to or more than 10-mg/kg body weight, and therefore, these total dose amounts would suffice for the majority of average-sized patients that develop MH.[1]

Over the past several decades there has been steady growth of free-standing or office-based surgery facilities that use intravenous anesthesia techniques without inhalational agents, and stock succinylcholine to treat life-threatening airway emergencies only. Over this period MHAUS has received numerous requests from anesthesiologists at many of these centers, as well as from representatives of the Ambulatory Surgery Committee of the American Society of Anesthesiologists, and the Society of Ambulatory Anesthesia, to amend our recommendations for stocking dantrolene in these facilities. These requests have been based on three main arguments. The first is the assumption that since the incidence of MH susceptibility in the general population is low, and the need for succinylcholine to treat an airway emergency in these centers is uncommon, then the likelihood of the above two events happening to the same patient is so low that it renders the cost of stocking dantrolene prohibitively high when compared to its potential usefulness.[2] The second is that accrediting agencies such as The Joint Commission and others have traditionally relied on the expert opinion of patient safety organizations such as MHAUS to determine accreditation criteria. These accreditation organizations, in line with MHAUS recommendations, have taken the

[1] http://www.mhaus.org/faqs/dantrolene

[2] At the time of this writing(2016), there are three dantrolene products on the market. Dantrium (Par Pharmaceuticals, Woodcliff Lake, NJ, USA) is one of the generic dantrolene products, is supplied as 20-mg vials (each mixed with 60 mL sterile water), has an approved shelf-life of 36 months, and costs $1,063 per year to stock. Revonto (US World Meds, Louisville, KY, USA) is one of the generic dantrolene products, is supplied as 20-mg vials (each mixed with 60 mL sterile water), has an approved shelf-life of 36 months, and costs $840 per year to stock. Ryanodex (Eagle Pharmaceuticals, Woodcliff Lake, NJ, USA) is the newer hyperconcentrated form of dantrolene, is supplied as 250-mg vials (each mixed with 5 mL sterile water), has an approved shelf-life of 24 months, and costs $3,450 per year to stock.

stance that surgical facilities must stock dantrolene if they also stock succinylcholine as a requirement to become accredited by the Center for Medicare and Medicaid Services (CMS).[3] The third is that to acquire accreditation, some ambulatory surgery facilities that do not want to incur the cost of dantrolene will not stock succinylcholine, thus putting their patients' lives at risk in the event of a life-threatening airway obstruction.[4]

Discussion:

MHAUS hotline consultants, members of our board of directors, and professional advisory council discussed at length the advantages and disadvantages of stocking dantrolene in these types of facilities and whether or not we should amend our existing recommendations. Opinions varied widely and generally fell into one of two approaches. The majority group of MH experts believes that as a patient advocacy organization that was originally chartered by MH susceptible patients and has MH susceptible families on our board of directors, the primary responsibility of MHAUS is to protect the health of our patients, both known MH susceptibles, and those who will subsequently develop MH, but are as yet unaware of their MH susceptible status. Experts in this group feel that the cost of stocking dantrolene, even if never used, is a relatively small price to pay for the security and confidence of knowing that anesthesiologists can be free to stock and administer succinylcholine for life-threatening airway obstruction without fear of patients developing MH without the only known antidote immediately available. These experts hold strong beliefs that one of the missions of MHAUS is to make an MH death a "never event", and that having an adequate supply of dantrolene wherever triggering agents are administered is crucial to this mission, especially in light of data that demonstrates a convincing relationship between the length of time it takes to administer dantrolene and subsequent patient outcomes. Data from the NAMHR indicate that the likelihood of an MH complication increased 1.6 times for every 30-minute increase in time between the first MH sign and the first dantrolene dose.[1] In data from Canada, the time between onset of the first clinical sign and dantrolene administration was longer in patients who experienced complications compared with those who did not (23.5 vs. 15.0 minutes, P = 0.005) and for each 10-minute delay in administration of dantrolene, complications increased substantially. When dantrolene administration was delayed beyond 50 minutes, complication rates increased to 100%.[2] Furthermore, there is an absence of existing reliable data on the incidence of MH susceptibility in different geographical areas, and on the incidence of the use of succinylcholine during administration of total intravenous anesthesia. Therefore, there is no way to approximate the true risk of MH in this clinical situation.

Other MHAUS experts, however, acknowledge the low incidence of MH caused by succinylcholine alone and the cost to health expenditures on a more global basis if every surgical facility was required to continuously buy and stock a dantrolene supply that is never used. This group of experts also worry about the health consequences of anesthetized patients if these surgical facilities choose not to stock succinylcholine solely for the reason to avoid the obligation of purchasing dantrolene, and they strongly oppose a recommendation that is not evidence-based. Some experts in this latter group thought that another reasonable option would be to require less than a full recommended dose (10 mg/kg) of dantrolene, reasoning that a "starter" dose would be useful prior to transferring the patient to a full service medical center.

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[3] https://www.ashp.org/news/2016/05/20/readiness_for_malignant_hyperthermia_can_be_survey_stumbling_block, Accessed December 11, 2017.

[4] This does not take into account the recent availability of sugammadex, which may facilitate the use of high-dose intravenous rocuronium to treat life-threatening airway obstruction.

Conclusions:

The consensus of our experts was that the incidence of MH induced by succinylcholine alone is not rare enough to justify the absence of dantrolene wherever succinylcholine may potentially be administered. Facilities that stock and have the potential to administer any triggering agent, including succinylcholine without volatile agents, should have dantrolene immediately available (i.e., the ability to administer dantrolene within 10 minutes of the first sign of MH) in the event that a patient in that facility develops MH. Organizations that inspect healthcare facilities on behalf of CMS, as well as individual state-based licensing and inspection agencies should be the purveyors of decisions that involve healthcare costs to society.

Please note: This recommendation was posted in 2018 based on information and data gathered in 2016/2017. Please see the MHAUS Recommendation Development Process link for more information: **https://www.mhaus.org/healthcare-professionals/mhaus-recommendations/the-mhaus-recommendation-development-process/**

For the most up to date pricing for dantrolene, please contact the manufacturer:

Dantrium® - PAR Pharmaceuticals

Revonto® - US WorldMeds

Ryanodex® - Eagle Pharmaceuticals

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Can Patients with a Suspected Personal or Family History of MH be Safely Anesthetized Prior to Diagnostic Testing for MH Susceptibility?

Poasted in 2018

Background:

Patients with a known or suspected personal or family history of MH are often denied access to general anesthesia prior to diagnostic testing for MH susceptibility, resulting in cancellation and postponement of necessary surgical procedures. Also, MH susceptible patients may be told they cannot have surgery in ambulatory surgery centers but must have surgery at inpatient hospitals.

Discussion:

A suspected personal or family history of possible MH is not uncommon in patients requiring general anesthesia for medical or surgical procedures.[1] The details of the presumed episode may be unclear, and in many instances, it is impossible to determine these details because medical records cannot be accessed in a timely manner. However, some patients suspected of being MH susceptible may require surgical management before formal MH susceptibility testing has been performed. Additionally, for many patients, diagnostic testing for MH susceptibility is not feasible because of the geographical distance to an MH biopsy-testing center, or their lack of insurance coverage for muscle contracture or genetic testing.

Conclusions:

Care of MH susceptible patients need not be restricted by the lack of formal MH susceptibility testing, nor should care be limited to inpatient hospitals facilities.[4] MH susceptible patients can be safely cared for in most anesthetizing locations, including appropriately staffed and resourced ambulatory surgery centers, provided non-MH triggering agents are used.[4] However, the chosen anesthetizing location should meet the following criteria: 1. The facilities should be prepared to recognize and treat an MH crisis [2,3,6,8,9] according to the established guidelines by MHAUS and accrediting organizations .[4,5] 2. Dantrolene should be accessible within ten minutes of the first signs of MH, and the facility should have the capacity to administer at least 10mg/kg of dantrolene in the event of an acute MH episode requiring multiple dantrolene doses to abort the crisis.[3,4] 3. The anesthesia machine should be flushed according to its specific manufacture's recommendations and/or charcoal filters placed on both inspiratory and expiratory limbs to minimize residual volatile agent in the circuit (http://www.mhaus.org/healthcare-professionals/be-prepared/preparing-the-anesthesia-machine/).[4,5] 4. There should be a formal agreement in place between ambulatory surgery centers and hospitals for transfer of patients to higher care after a suspected MH episode.[4,5]

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What evidence-based interventions are recommended to alleviate hyperthermia associated with Malignant Hyperthermia?

Posted in 2018

Background:

The most important treatment of Malignant Hyperthermia (MH) is discontinuing MH triggering agents, hyperventilation, and timely administration of dantrolene. However, prolonged hyperthermia worsens patients' outcomes[1] and should also be treated when occurs.

Many cooling strategies are available, but in practice it is impossible to implement all of them simultaneously without distracting from the key tasks of administering dantrolene and treating the patient's metabolic and respiratory abnormalities.

Many experts believe that hyperthermia is a sign of inadequate physiological treatment and clinicians' priority should be to stop MH with dantrolene and adequately treat hypercarbia and acidosis before focusing time and efforts on thermal management (personal communication, Dr. Daniel Sessler). It is therefore important to prioritize cooling approaches based on efficiency, ease of use, and safety.

Discussion:

Thermal management can be divided into three categories: pharmacologic, noninvasive, and invasive. *Pharmacologic* treatment of hyperthermia includes dantrolene, acetaminophen, and nonsteroidal anti-inflammatory drugs. Dantrolene is the only clinically available specific treatment for MH and, after discontinuation of triggering agents, should always be the initial treatment for any suspected MH episode. The recommended initial dose of dantrolene is 2.5 mg/kg bolus with repeated boluses as needed until hypermetabolism is controlled.

Acetaminophen, especially now that it is available intravenously, is increasingly used for analgesia and treatment of fever. However, its effectiveness in treating hyperthermia caused by MH has not been determined. Similarly, the role of nonsteroidal anti-inflammatory drugs as antipyretics during MH remains unknown. Nonetheless, the high body temperature associated with MH is due to excessive heat production by skeletal muscle; there is thus no theoretical basis, much less evidence, to suggest that antipyretic drugs will help control hyperthermia during MH episode.

Noninvasive treatments of hyperthermia include strategic ice packing, forced air cooling, circulating cool water blankets, cold intravenous fluids, and ice-water immersion. Cold intravenous fluid is effective: in healthy volunteers, 40 mL/kg infusion of 4°C or 20°C fluid, core temperature transiently decreased 2.5 ± 0.4°C and 1.4 ± 0.2°C, respectively.[2] Cold fluids should be kept available and should typically be the initial cooling measure during an MH crisis, especially since hydration is usually appropriate to limit the risk of renal injury from myoglobinemia. The method is limited by the amount of intravenous fluid that can be safely administered, typically about three liters in adults.

Ice packing (neck, groins and axillae) is effective, although prolonged direct skin exposure may provoke tissue injury. Convective cooling with forced air at ambient temperature is easy to implement and essentially risk-free. However, the method is nearly ineffective and little better than simply removing all covers and exposing the patient to ambient air. Ambient air temperature should be lowered to the extent practical.

Circulating cool water blankets set to low temperatures such as 4°C absorb considerable heat,[3] but are not available in all operating rooms and positioning water blankets or mattresses during an MH crisis may be complicated and distracting. As with any surface cooling method, efficacy is a linear function of surface area used. Some temperature management systems use circulating water with pads that feature thin hydrogel coating. They are more effective blankets than conventional circulating-water because they contact the skin well and have low thermal resistance.

Ice water immersion is by far the most effective external cooling method,[4] but is limited by the equipment required and need to move patients. In practice, immersion is not an approach that can be organized and implemented safely in the midst of an MH crisis.

Invasive strategies include bladder, rectal, gastric or peritoneal lavages, esophageal heat exchangers, intravascular heat exchange devices, and cardiopulmonary bypass. Gastric lavage is neither effective nor safe due to low return of aspiration of the injected fluids.[4] Bladder lavage is ineffective due to small contact surface area and a relatively low bladder perfusion.[4] Although not studied, rectal lavage may have similar limitations. Peritoneal lavage is highly effective because the peritoneum has a large contact surface area and is highly perfused. However, it should be noted that this method is invasive and requires special apparatus and skills (often available in emergency departments).

An esophageal heat exchanger is a new device which is inserted much like a standard orogastric tube. It has additional connectors designed for standard water blanket chillers/heaters. The device provides heat exchange via the blood circulation surrounding the esophagus. The system extracts about 50 watts which is relatively small compared to potential heat production during a severe MH crisis.[5] Furthermore, the device is not yet commonly available. Lastly, cardiopulmonary bypass is by far the most effective cooling device, but its invasiveness and technical challenges are an obvious deterrent to recommending its application during an MH crisis unless bypass is required to treat hyperkalemic cardiac arrest. Furthermore, the degree of cooling is very rarely required.

Conclusions:

Cooling should never distract from dantrolene administration and hyperventilation. Most patients treated promptly with dantrolene and hyperventilation do not become seriously hyperthermic or necessitate active cooling. Active cooling should be used with care since there can be a substantial after-drop, depending on the cooling technique, duration of application, and body heat distribution; cooling should thus be discontinued when core temperature decreases to 38°C.

External cooling methods such as circulating-water mattresses or ice packs should be considered first. If external cooling is insufficient, an easy, effective, and safe next cooling strategy is to infuse 20 mL/kg of refrigerated intravenous fluid. Other treatments should rarely be necessary, but peritoneal lavage is probably the safest and most effective of the invasive

approaches if the peritoneum is already open or the patient is in an emergency department with the requisite equipment and skills.

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Masseter Muscle Rigidity (MMR): Definition, Relationship to Malignant Hyperthermia (MH), and Management

Posted in 2018

Background:

MMR can be generally defined as a marked difficulty in manual mouth opening that interferes with and impedes direct laryngoscopy and tracheal intubation without the presence of temporomandibular joint dysfunction. When MMR occurs in response to administration of succinylcholine in the absence of an underlying temporomandibular joint disorder or myotonia, it may be an initial sign of MH[1-4]. As early as 1969, Gibson et al reported two cases where they described the severe nature of the rigidity of masseter muscles when MMR occurs[5, 6]

Discussion:

Confusion often arises when diagnosing MMR due to its similarity with the normal but variable degree of increase in masseter muscle tension that may occur after succinylcholine administration in healthy patients [6-8]. This is an inherent characteristic of succinylcholine administration and has also been linked to administration of subclinical doses in children[9, 10]. To differentiate between the normal rises in masseter tension versus a case of true MMR, assessing masseter rigidity is helpful. The term 'jaws of steel' (coined by Kaplan et al[11]) aptly emphasizes the severe nature of the rigidity. When MMR occurs, it may be both a harbinger of acute MH and/or associated with clinically significant rhabdomyolysis[1-4, 12, 13]. Therefore, clinicians should seek other concomitant signs of the presence of acute MH, such as tachycardia or hypercarbia that are inappropriate for the clinical situation, generalized trunk or limb rigidity, hyperthermia, cola-colored urine indicative of myoglobinuria, and/or peaked T waves or other arrhythmias consistent with hyperkalemia. However, in some patients who have subsequently progressed to MH, those signs did not appear immediately after MMR appearance. Sufficient evidence exists in the literature of cases in which MH ensued following MMR that it is prudent to cancel elective surgery when MMR occurs[1-4]. If the surgical procedure is emergent, then a non-MH triggering anesthetic should be instituted. Whether or not the case is cancelled, several hours of careful observation for additional signs of MH are warranted. This approach of employing non-triggering anesthetic in emergency cases, was first reported in a definitive fashion by Donlon et al in 1978[14] and later by others[15, 16]. The anesthesia provider should obtain a blood sample to screen for metabolic acidosis, hyperkalemia, and elevated creatine kinase levels. A urine sample should also be obtained to check for heme, which if positive without microscopic red blood cells may represent either myoglobinuria or hemoglobinuria. Serum creatine kinase measurements (CK) should follow immediately after and at 6-8 hours. CK may not be elevated immediately following MMR with peak levels not achieved until 12 to 24 hours following succinylcholine administration[17]. If CK is greater than 5 times the upper limit for normal value, then appropriate treatment for rhabdomyolysis, including measures to prevent acute damage to the kidneys from myoglobinuria should be instituted [18]. While cola colored urine and elevated creatine kinase may occur following MMR, development of any other additional signs of MH should prompt immediate dantrolene administration and other adjunctive therapies[1]. In patients who

have myotonia, administration of succinylcholine may result in MMR and rigidity of the total body[19, 20]. Prior history of myotonia is the most helpful factor in differentiating between MMR and myotonic contractures

Conclusions:

MMR may be the first sign of an acute MH event. However, no conclusive data exist for clinicians to determine the likelihood of developing MH after an episode of MMR. If no other signs of MH are observed, the patient may still be at risk for developing clinically significant rhabdomyolysis and should be observed and treated as necessary. Patients who develop rhabdomyolysis without other signs of MH should be referred to a neurologist to rule out underlying myopathies. If no myopathies are found, evaluation for MH susceptibility may be indicated (https://www.mhaus.org/testing/introduction-to-mh-testing/). When an anesthetic is necessary in patients who experienced MMR during a previous anesthetic but have not had a full evaluation for MHS or myopathy, such patients should receive a non-triggering anesthetic for their procedure. Caveat: No MH or neurologic workup is indicated if no postoperative rhabdomyolysis or signs of MH occur and the patient informs the anesthesiologist that he/she has a history of temporomandibular joint disorder and/or his/her post-anesthetic examination reveals an inability to open the mouth well.

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