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Title

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Journal

Proceedings of UCLA Health, 21(1)

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Publication Date

2017-11-02

CLINICAL VIGNETTE

Acute Appendicitis in a Patient with a Family History of Malignant Hyperthermia

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Case

A 28-year-old male with past medical history of asthma presented to the emergency room with one day of right lower quadrant pain and subjective fever. Initial vital signs were within normal limits, notably afebrile, and heart rate (HR) 76 beats/minute. Laboratory evaluation was remarkable for leukocytosis (WBC 14), creatinine 1.4 mg/dL, and blood on urinalysis. A computed tomography (CT) scan of the abdomen and pelvis without contrast was read as acute uncomplicated appendicitis. He was scheduled for urgent open appendectomy. Subsequent evaluation by an Anesthesiologist revealed that the patient's father had a confirmed history of malignant hyperthermia (MH) in addition to two siblings with "similar" problems with anesthesia.

The patient was brought to the operating room with plan for spinal anesthesia with non-MH triggering medications. Prior to his arrival, the anesthesia machine was prepared by removing volatile anesthetic vaporizers, replacing carbon dioxide (CO₂) absorber with a new canister, and flushing the anesthesia circuit for one hour. Initial patient vital signs in the operating room were blood pressure (BP) 122/74 mmHg, HR 75 beats/minute, respiratory rate (RR) 18 breaths/minute, oxygen saturation (SpO₂) 100% on room air, and temperature 34.5°C measured at the axilla. The patient underwent uncomplicated placement of spinal anesthesia with 12.75 milligrams (mg) of 0.75% hyperbaric bupivacaine and 20 micrograms (mcg) of fentanyl with documented T6 dermatomal level. Intravenous (IV) sedation with fentanyl, midazolam, and propofol was then administered. Approximately twenty minutes after the start of surgery, anesthesia was converted to general anesthesia due to patient agitation and reported pain at the surgery site. Patient underwent rapid sequence induction with IV propofol and rocuronium and was intubated and placed on mechanical ventilation without difficulty. Total intravenous anesthesia (TIVA) was maintained with propofol infused at 150mcg/kg/min and intermittent boluses of IV hydromorphone. After induction of general anesthesia heart rate notably increased to 90-100 beats/minute and initial esophageal temperature was 38.0°C. BP and SpO₂ remained stable and within normal limits. End tidal carbon dioxide (ETCO₂) was 34 mmHg at a minute ventilation (V_E) of 7.7 L/minute. A left radial arterial catheter was placed after induction for serial arterial blood gas (ABG) monitoring. Initial ABG results on 100% Oxygen (FiO₂) were pH 7.32, PaO₂ 479 mmHg, PaCO₂ 37

mmHg, HCO₃ 19 mmol/L, base excess (BE) -7 mmol/L, lactate 3.8 mmol/L. A 1 liter (L) bolus of cold IV normal saline intraoperatively reduced temperature to 37.4°C. Surgery finished approximately one hour after induction of general anesthesia. Surgery noted frankly gangrenous appendix walls, but no perforation was identified. Intraoperatively, a total of 1.3 L of IV lactated ringers and 1 L of IV normal saline was given. Estimated blood loss was 30 ml, and urine output was 75 ml, which was noted as "tea-colored."

The patient was brought to the post anesthesia care unit (PACU) intubated and mechanically ventilated due to concern for progressing sepsis and acidosis. On arrival to the PACU vital signs were stable, except for low grade sinus tachycardia, HR 105 beats/min, and afebrile. IV sedation was maintained with a propofol and fentanyl infusion. Approximately hours later, he acutely became febrile up to 39.2°C with increased tachycardia, HR 125 beats/min. He was given acetaminophen 650 mg per rectum, 1 L normal saline IV bolus, and a cooling blanket. Metronidazole and cefepime were ordered by general surgery for antibiotic coverage. ABG analysis revealed a mixed respiratory and metabolic acidosis, pH 7.27, PO₂ 353 mmHg, PCO₂ 45 mmHg, HCO₃ 20 mmol/L, BE -7 mmol/L on FiO₂ of 1.0, and a V_E of 5.4 L/min. V_E was increased to 7.2 L/min. Subsequent ABG analysis revealed resolution of respiratory acidosis, PCO₂ 33-39 mmHg but with continued metabolic acidosis, HCO₃ 18-19 mmol/L and BE -6 mmol/L. Creatinine kinase (CK) was elevated at 377 IU/L. The malignant Hyperthermia Hotline was contacted in the PACU, but the clinical situation determined to be low probability of MH by consultant and no treatment with dantrolene was recommended.

On post-operative day one (POD 1), patient's clinical situation remained guarded in the intensive care unit with continued fever, up to 40.3°C, and sinus tachycardia. ABG showed persistent metabolic acidosis, pH 7.32, HCO₃ 17 mmol/L, BE -7 mmol/L. Respiratory alkalosis, PaCO₂ 30-39 mmHg, was maintained on mechanical ventilation with elevated V_E of 11 L/min. CK continued to increase to 1158 IU/L. Urine output remained adequate but notably "tea-colored." The Malignant Hyperthermia Hotline was again contacted and the consultant, the same from the prior day, was updated of the patient's clinical situation. The consultant now recommended treatment with dantrolene given the patient's overall poor clinical state. Dantrolene (Dantrium) 2.5 mg/kg was administered through a

peripheral IV catheter and a subsequent dose of 1 mg/kg was given six hours later.

The following day, POD 2, the patient's overall clinical status had improved. He was afebrile with resolution of sinus tachycardia. Metabolic acidosis improved on ABG, pH 7.34, PCO₂ 39 mmHg, HCO₃ 21 mmol/L, BE -4 mmol/L, and CK decreased to 517 IU/L. The patient was extubated uneventfully later that day and discharged home on POD 5 with planned outpatient follow up with general surgery.

The patient presented to the emergency department on POD 7 with complaints of scrotal swelling and left upper extremity swelling, erythema, and tenderness. Scrotal edema was determined to be iatrogenic from fluid resuscitation from recent hospitalization. A transthoracic echocardiogram was normal ruling out cardiogenic cause of hypervolemia. He was diuresed with IV furosemide with resolution of scrotal edema. A left upper extremity ultrasound revealed an occlusive thrombus extending from the brachial vein to the distal axillary vein. Thrombus was thought to be provoked from recent surgery and immobilization. He was initially treated with a IV heparin infusion and later converted to oral warfarin. Patient was discharged home on POD 9 with plan for three months of warfarin anticoagulation for treatment of left upper extremity thrombus.

Discussion

Malignant hyperthermia (MH) is a feared complication of anesthesia triggered by halogenated gases and succinylcholine with risks of significant morbidity and mortality. However, the constellation of symptoms that constitute this disease can be vague and often overlaps with other conditions.¹ A grading scale was developed by Larach et al² and published in *Anesthesiology* in 1994. It highlights at least six processes associated with MH (rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement, and family history) and assigns points to specific indicators within each category in order to describe likelihood of a true MH diagnosis on a six point scale. In the case of our patient, we scored this patient as almost certainly having MH. The authors acknowledge, however, the scale works on a continuum: aborting a case at the earliest concern for MH may score differently than allowing the case to continue and may alter the vital signs, physical findings, and lab values measured.

Fever in general is a nonspecific sign, often noted later in suspected MH but variable in appearance.³ Numerous causes for elevated body temperature exist, and the clinician must distill from available information the most likely etiology. Infection and sepsis are well known causes, as are primary CNS causes including brain structure abnormalities, stroke, meningitis, and rare prion diseases. Illicit drugs like cocaine, MDMA, amphetamines, and phencyclidine have all been associated with fever, both with acute toxicity and withdrawal.

More common medications, including those leading to neuroleptic malignant syndrome and serotonin syndrome may lead to fever. Allergic reactions, transfusion reactions, endocrinopathies, and heatstroke must be considered, as well as more exotic causes such as tick-borne illness and snake venom. Treatment options certainly vary based on likely cause.

Dantrolene is the mainstay treatment for MH, but the decision to institute its use can be challenging.⁴ Its mechanism of action by binding to RYR1 receptor and reestablishing an equilibrium between release and uptake of calcium from the SR¹ is specific to MH and MH-type disease; it is unhelpful in the treatment of other diseases. Additionally, the cost and lack of clinician familiarity may delay initiation of therapy and also requires ongoing administration. In cases of doubt, it is important to remember that the MH hotline is available 24 hours a day and can be utilized to discuss complicated cases. Ultimately, the anesthesiologist must use his or her best judgment in the treatment of the patient.

While early detection and standardized treatments of MH have reduced mortality rates, the postoperative course of MH after treatment with dantrolene is less well-described due to the relatively low occurrence of the event.⁵ For example, the rapid intravenous administration of dantrolene through a peripheral IV catheter may have led to the development of an upper extremity venous thrombus in our patient.⁶ Each vial of Dantrium contains dantrolene 20 mg and mannitol 3000 mg and requires reconstitution in 60 ml of sterile water and shaken until clear. Our 70 kg patient received a total of dantrolene 245 mg and mannitol 36,750 mg in 735 mL sterile water through his peripheral IV catheter. Mannitol has been shown to be an independent risk factor for upper extremity DVTs when administered through a peripheral IV catheter⁷ and data from the North American Malignant Hyperthermia Registry lists a 9% incidence of phlebitis in the setting of dantrolene.⁸ Phlebitis has been shown to be an independent risk factor for the development of thrombosis.⁹ Although MH is associated with the expression of inflammatory mediators that can promote thrombogenesis,¹⁰ there is no current evidence that links MH directly with a hypercoagulable state. MH is a life-threatening emergency and dantrolene administration should not be delayed due to concern for vascular complications; however, consideration may be warranted for administration through a large-bore peripheral IV catheter or central venous catheter if present.

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