Abnormal Presentation of Suspected Malignant Hyperthermia Secondary to Propofol and Rocuronium in a 25-Year-Old Male

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ABSTRACT

Malignant hyperthermia (MH) is a rare hypermetabolic condition involving calcium regulation within the skeletal muscle. This case is important as an educational example of how variable the presentation of malignant hyperthermia can be in an individual with no prior personal or family history. This case is also unique in that the anesthetic (propofol) and the paralytic (rocuronium) medication used during the procedure are considered safe and rarely ever associated with causing MH. The patient presented in this case is a 25-year-old white male who was brought to the emergency department following a motor vehicle collision. After receiving propofol, rocuronium, and treatment for multiple fractures by orthopaedics, the patient began to develop symptoms resembling those of MH during the end of the case. He was treated per MH protocol with dantrolene, temperature control, and transferred to the Surgical Intensive Care Unit (SICU) for observation. He eventually recovered, was discharged home, and told to follow up in clinic in one week. It is important to note that even when using anesthetics or paralytics deemed "safe," MH can present with any combination of its symptoms at any time during or after a surgical case.

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INTRODUCTION

Malignant Hyperthermia is condition that involves a defect in the calcium regulation of the skeletal muscle. The defect is found in the ryanodine receptor, which directly regulates calcium release from muscle.[1] Of the two genes currently identified to cause MH, 70% of cases are due to a mutation in the *RYR1* gene, which codes for the ryanodine receptor, while 1% is caused by a defect in the *CACNA1S* gene, which codes for the skeletal muscle calcium channel.[2] When susceptible patients are exposed to depolarizing muscle relaxants or volatile inhalational anesthetics, the defective ryanodine receptor leads to an intramuscular buildup of calcium resulting in a substantial metabolic reaction. The clinical symptoms can include any combination of hypoxemia, hypercapnia, tachycardia, muscle rigidity, acidosis, hyperkalemia, and/or hyperthermia.[3] We describe the recognition and treatment of a

patient who had late onset of symptoms corresponding to MH, following two surgeries for trauma caused by a motor vehicle collision.

CASE PRESENTATION

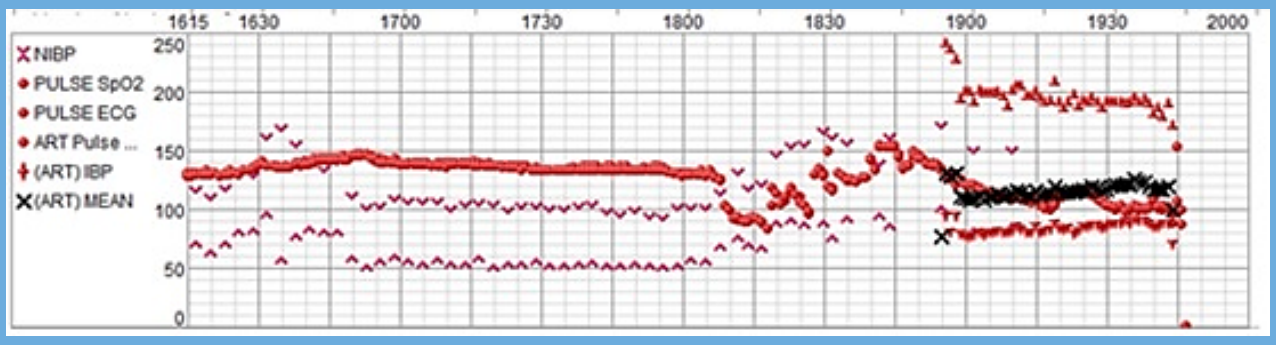
A 25-year-old white male presented to University of Arkansas for Medical Sciences (UAMS) hospital with a chief complaint of right hip pain, facial pain, and left hand pain. The patient was involved in a motor vehicle collision where he fell asleep at the wheel. He had loss of consciousness at the scene. The patient sustained a right hip fracture/dislocation that was reduced in an outside hospital. He presented to UAMS the same day after stabilization for definitive surgical management. During initial evaluation after transfer, the patient had no new complaints. Patient denied any allergies, past medical or surgical history. Current home medications only included cetrizine 10mg taken by mouth daily. The plan was to take the patient back the same day for operative intervention.

Preoperative physical exam showed a 75.75 kg (167 lb) well-nourished white male in no acute distress. Upon arrival vitals included a blood pressure (BP) of 120/74 mmHg, pulse of 98 beats/minute (bpm), temperature of 98.6° F (37° C), respirations of 16 breaths/minute, and saturation of peripheral oxygen (SpO2) of 95%. Head exam showed a laceration on the left upper lip that was closed at an outside hospital, nasal deformity, and a small laceration in mouth. Pulmonary exam revealed non-labored and clear breath sounds. Cardiovascular exam revealed regular rate and rhythm, with good perfusion. Left upper extremity exam revealed a left wrist splint with sensation intact to fine touch and two point discrimination, but reduced range of motion due to splint. Capillary refill was less than 2 seconds and radial and ulnar pulses were 2+ with normal Allen's test after splint was removed. Right lower extremity exam was positive for tenderness to palpation on right hip and with log roll, decreased sensation to touch in all toes, and inability to move right foot. Capillary refill was less than 2 seconds with palpable dorsalis pedis pulses. Preoperative basic metabolic profile was within normal limits, and complete blood count (CBC) was significant for a hemoglobin of 12.9 g/dL and a hematocrit of 38.4%. Plain radiographs showed left hand with a comminuted 5th metacarpal base fracture and a right hip with an oblique comminuted fracture of the femoral head (Pipkin classification 1-2). Pre-anesthesia evaluation was only significant for limited opening of mouth and some tongue swelling secondary to the accident.

Once patient was stabilized he was taken to the operating room for open reduction and internal fixation (ORIF) of his right femur and percutaneous pinning of his left hand. Patient had standard monitors placed, peripheral IVs placed in both antecubitals, and was premedicated with 2mg midazolam. He was then sedated with 250 mcg fentanyl, 80 mg 2% lidocaine, 200 mg propofol, and 50 mg rocuronium. Patient was intubated, with endotracheal tube placement being confirmed with end tidal carbon dioxide ($ETCO_2$) and auscultation of bilateral breath sounds. Pre-procedure vitals were included a BP of 125/86 mmHg, pulse of 110 bpm, respiration of 18 breaths/minute, temperature of 99.4° F (37.4° C), SpO2 of 96%, and $ETCO_2$ of 37.7 mmHg. Ventilator mode was set at a tidal volume of 525 mL, respiratory rate of 12 breaths/minute, positive end expiratory pressure (PEEP) of 5 cm H_2O. The first procedure to repair the right femur was started one hour after intubation (13:23) and lasted for three hours with minimal change in vitals. Procedure for repair of left hand then began at 16:53. Tourniquet was inflated and then deflated at 17:09 and 17:55 respectively. The orthopaedic hand team finished the procedure and closed at 18:05, leading to a total proce-

dure time of approximately 4 hours and 18 minutes. During the surgery it was noted by the hand team that the patient's extremities seemed abnormally rigid, but this was attributed to possible arousal of the patient since it was near the end of surgery. During the two procedures the patient received a total of 350 mg propofol, 250 mcg fentanyl, 200 mg rocuronium, 3 mg neostigmine, and 1000 mL normal saline. Patient also had a total urine loss of 1619 mL of clear urine and an estimated blood loss of 100 mL.

At 18:36 the patients $ETCO_2$ elevated to 82 mmHg and remained elevated despite increased ventilation and temperature increased to 101.84°F (38.8°C). The patient became tachycardic with a rate of ~150 bpm, and hypertensive with a mean arterial blood pressure of approximately 130 mmHg. Anesthesia providers in the room checked the filter on the anesthesia gas machine to see if that could be the problem. Once it was decided that the machine and instruments were working optimally, they called for help and multiple anesthesiologists quickly responded. During this time it was noted that the patient's extremities were very rigid and he had associated masseter rigidity (Figure 1). MH protocol was then initiated: dantrolene was administered, the national MH hotline (1-800-644-9737) run by the Malignant Hyperthermia Association of the United States (MHAUS) was called, cooling with ice packs was applied over cooling blanket, the suspected volatile agent rocuronium was discontinued, and circuit on the anesthesia machine was changed. Propofol was started and an arterial line was placed. Arterial Blood Gas (ABG) and labs were obtained after a dantrolene bolus was given. A total of 200 mg dantrolene was given. $ETCO_2$ approached normal levels, and patient's heart rate, BP, and temperature decreased. Active cooling was ceased once patient's temperature fell below 100.4° F (38° C). After consulting an MH expert on the MHAUS hotline, patient was transported with stable vital signs to



NIBP- Noninvasive Blood Pressure; (ART) IBP- Arterial Invasive Blood Pressure; (ART) MEAN- Average Arterial Blood Pressure; X-axis=time, Y-axis= millimeters of mercury (mmHg)

SICU with American Society of Anesthesiologist (ASA) standard monitors and intubated on positive pressure ventilation (PPV) with 100% fraction of inspired oxygen (FIO2). While being kept overnight in the SICU, the patient remained intubated and sedated on versed and fentanyl, cooled with a cooling blanket, and additional rounds of dantrolene were given with patient's highest temperature reaching 102.7° F (39.27° C). Without any further notable events, the patient was discharged home a week after surgery with pain medications, antibiotics, anticoagulation, and scheduled follow up with the orthopaedic trauma clinic. He recovered well.

DISCUSSION

MH is a dangerous but rare syndrome with an incidence of 1 in 62,000 procedures when using a combination of anesthetic agents with paralytics.[6] The mortality of MH can reach as high as 70-80% if left untreated, but when suspected and treated properly (IV dantrolene, body temperature control, etc.) the mortality drops to less than 5%.[7] The treatment of MH is focused at reversing the symptoms created by the excess calcium and activity within the skeletal muscles. Dantrolene depresses excitation-contraction coupling in skeletal muscle by directly binding to the ryanodine receptor and decreasing free intracellular calcium concentration.[11] The cooling blanket and chilled IV saline are focused at lowering the body temperature to prevent harm.

This particular case demonstrates how MH can be variable with the exact time during a surgery it may present in patients. The normal time most cases of MH symptoms have been documented range from within the first 10 minutes of the case to some initial signs appearing as late as an hour into the case depending on which anesthetic and paralytic is used.[8] This case is interesting as the patient's onset of symptoms was well later than the average at approximately 270 minutes into surgery after being treated with two agents (propofol and rocuronium) that are usually not associated with instigating malignant hyperthermia.

Larach et al. use a scale developed by an international panel of MH experts which ranks the "qualitative likelihood that an adverse anesthetic event represents malignant hyperthermia and that, with further investigation of family history, an individual patient will be diagnosed as malignant hyperthermia susceptible."[4] This patient was a delayed class 6 on the MH scale with a grade of 68 points. Class 6 is the highest on the MH grading scale defined by Larach et al. indicating "almost certain MH" for any score ≥ 50.[4] This scale uses seven categories that clinicians use today to grade suspected MH: rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement, family history, and "other indicators." This patient scored a 68 on the grading scale after developing masseter spasm (15 points), generalized muscle spasm (15 points), P_{CO2}>55mmHg (15 points), inappropriate rapid increase in temperature (15 points), inappropriate sinus tachycardia (3 points), and reversal of symptoms with administration of dantrolene (5 points). Interestingly, the patient had no family members with a history of potential MH.

The drugs used during sedation are very important when monitoring a patient for MH, and the most common ones associated with MH should be well known to the anesthesiologist or certified registered nurse anesthetist (CRNA). According to MHAUS, the common drugs associated with MH include: general inhaled anesthetics, desflurane, enflurane, ether, halothane, isoflurane, methoxyflurane, sevoflurane, and succinylcholine.[9] Our patient received propofol and rocuronium which MHAUS explicitly mentions as safe and unassociated with instigating

MH in patients.[10] This case is not the first one ever documented of rocuronium or propofol being associated with MH. There are two cases of patients presenting with MH described by Beggs et al.; both underwent treatment for suspected MH after their temperatures began to rise, 36 hours for one patient and 4 days for the other, after receiving rocuronium and propofol.[5] These two patients presented with the common initial symptoms of rising temperature and increasing $ETCO_2$. Our patient differs from these cases because although the same agents were used, his initial symptoms of muscle rigidity are not commonly seen until later during the presentation. This case demonstrates that rocuronium and/or propofol can possibly instigate MH in a susceptible patient, but the symptoms may not always be characteristic of the average MH presentation.

Another important aspect of this case is the symptoms with which the patient presented. The natural history of MH usually involves a patient, likely with family members with a history of MH events, who presents with symptoms such as rising $ETCO_2$ or body temperatures within the first hour of being exposed to a general anesthetic or depolarizing neuromuscular paralytic. As previously described, this patient did qualify according to MH grading criteria but MH is increasingly documented as having many different combinations of the aforementioned criteria. Larach et al. describes that unexplainable hypercarbia is the most common initial symptom of MH followed by sinus tachycardia and masseter muscle spasm.[4] This patient instead had apparent muscle rigidity approximately an hour and a half prior to any detected increase in $ETCO_2$. It is important for diagnostic purposes that clinicians are flexible when suspecting MH in a surgical patient, maintaining a heightened awareness when any of the signs are noted.

Malignant hyperthermia is an event that can be just as variable with when it presents as the symptoms that patient actually presents with. It is important to note that the earliest symptoms in this particular patient were not first recognized by the anesthesiologist, but instead by the surgeon and assisting medical student, highlighting the importance of good communication in a health care setting. All health care providers need to be aware of the signs and symptoms of MH and to have a low threshold for diagnosing the disease. Early diagnosis and treatment of MH is vital for good outcomes, because any time lost in making the diagnosis could become life threatening for the patient.

LEARNING POINTS

- Malignant hyperthermia (MH) is a rare hyper-metabolic condition secondary to a defect in the ryanodine receptor, which directly regulates calcium release from muscle. When susceptible patients are exposed to depolarizing muscle relaxants or volatile inhalational anesthetics, the defective ryanodine receptor leads to an intramuscular buildup of calcium resulting in a substantial metabolic reaction.
- MH clinical symptoms can include any combination of hypoxemia, hypercapnia, tachycardia, muscle rigidity, acidosis, hyperkalemia, and/or hyperthermia.
- Clinicians should vigilantly monitor for signs of MH regardless of drugs administered, as MH can occur with drugs assumed to be "safe."

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