Malignant hyperthermia resolving with discontinuation of sevoflurane alone

Abdullah Abolkhair,
Christian Seefelder[1]

*Department of Anesthesiology,
St. Elizabeth's Medical Center,
Boston, [1]Perioperative and Pain
Medicine, Children's Hospital
Boston, 300 Longwood Avenue,
Boston, Massachusetts, USA*

Address for correspondence:
Dr. Christian Seefelder,
Department of Anesthesiology,
Perioperative and Pain Medicine,
Children's Hospital Boston,
300 Longwood Avenue, Boston,
Massachusetts, USA.
E-mail: christian.seefelder@
childrens.harvard.edu

A B S T R A C T

An otherwise healthy 13 year old developed hypercarbia and increased temperature during anesthesia with sevoflurane. Discontinuation of sevoflurane, surface cooling, and hyperventilation resulted in prompt resolution. However, hyperkalemia continued to raise the suspicion for malignant hyperthermia, which was ultimately confirmed by ryanodine receptor gene sequencing. The case underlines the importance of intraoperative monitoring of end-tidal CO2 and temperature and the potential benefits of early discontinuation of inhalational anesthetics in the presence of signs and symptoms suspicious for malignant hyperthermia. The severe hyperkalemia suggests that standard guidelines for diagnosis and treatment of malignant hyperthermia, including dantrolene treatment, should be followed whenever malignant hyperthermia is suspected.

Key words: *Dantrolene, hypercapnia, malignant hyperthermia, ryanodine receptor, sevoflurane*

INTRODUCTION

Malignant hyperthermia (MH) is a potential complication from the use of succinylcholine and inhalational agents in susceptible patients. Dantrolene is the recommended effective treatment for MH. We report an anesthetic course that was later confirmed as sevoflurane-induced MH, which resolved by discontinuation of the agent alone.

CASE REPORT

Our patient was a 13-year-old female who had sustained an open right forearm fracture during gymnastics and required emergent orthopedic repair. She was otherwise healthy by history, on no medication, weighed 43 kg, and had no known allergies. There was no family history of anesthesia or of any medical problems that might have been relevant to her anesthetic care. She received intravenous (iv)

midazolam for anxiolysis. Anesthesia was induced with propofol and fentanyl. Rocuronium was administered for muscle relaxation and she was easily intubated. Anesthesia was maintained with sevoflurane in 50% oxygen and air. Intravenous cefazolin was administered and she was also given iv morphine. Over the first 20 minutes after induction her blood pressure, heart rate, and temperature decreased. Increased end-tidal CO_2 ($EtCO_2$) was noted [Table 1] and ventilation was increased. $EtCO_2$ continued to rise over the next hour in spite of doubled minute ventilation. The heart rate increased to 100/minute and there was mild hypotension, which was treated with additional iv crystalloid infusion; the patient's temperature also increased to 38.2°C. There was no other obvious explanation for the changes and so with MH in mind but without concerns regarding vital signs, sevoflurane was discontinued, fresh gas flows were increased to 10 L/minute, ventilation was changed from pressure-controlled to volume-controlled ventilation, and anesthesia was changed to iv propofol and opioids. Bispectral index monitoring was added. Active cooling was instituted with a forced-air warmer set on ambient temperature. Within 30 minutes, $EtCO_2$ and required minute ventilation decreased and all vital signs returned to normal, reassuring us. An arterial blood gas (ABG) was drawn at that time to rule out mixed acidosis. We were expecting normal results but it revealed slightly elevated lactate and hyperkalemia

Table 1: Vital signs and laboratory results during the perioperative course of the patient's malignant hyperthermia episode

Time since induction	Preop	Induction	20 minutes	90 minutes	2 hours	3 hours	4 hours	8 hours	POD1	POD2
Event		Induction		Intervention: change to TIVA		End of case	ICU admission			Discharge home
Heart rate (per minute)	118	120	70	100	90	78	118	99	90	58
Blood pressure (mm Hg)	110/74	120/80	90/40	78/40	110/55	113/61	121/84	111/55	115/58	109/68
Temperature (°C)	36.5	37.5	37	38.2	37.6	37	36.2	37.5	37.1	37.1
End-tidal CO_2 (mm Hg)	–	35	46	56	35	41				
Ventilation (L/minute)	Spont	5.3	6.2	10	6	6	Spont	Spont	Spont	Spont
Respiratory rate (per minute)	20	–	12	20	12	12	16	18	13	20
Arterial blood gas (pH/ p_aCO_2/p_aO_2)	–	–	–	–	7.41/35/176	7.42/36/341	–	–	–	–
Inspiratory oxygen (%)	–	–	–	–	50	50	–	–	–	–
Base excess (mmol/L)	–	–	–	–	-0.6	0.7	–	–	–	–
Lactate (mmol/L)	–	–	–	–	3.9	2.2	–	–	–	–
Potassium (mmol/L)	–	–	–	–	7.24	6.69	3.8	3.6	4.3	4.3
Creatinine kinase (U/L)	–	–	–	–	764	–	1189	1106	793	620

Spont = Spontaneous respiration; ABG = Arterial blood gas; POD = Postoperative day#; TIVA = Total intravenous anesthesia

of 7.2 mmol/L [Table 1], which persisted at 6.6 mmol/L 1 hour later at the time of completion of the surgery. The T-waves remained normal throughout. No muscle rigidity was noted by the anesthesiologists or surgeon at any time. In view of the rapidly resolving clinical picture, surgery was completed and no other specific treatment was instituted. However, we took samples for estimation of urine myoglobin and plasma creatinine kinase (CK). The patient was extubated and transferred to the intensive care unit (ICU) for monitoring. At this time, the patient and family were informed of the events, of the clinical diagnosis of MH, and that the patient and family members would have to be considered MH susceptible. The patient remained hemodynamically stable and potassium, lactate, myoglobin, troponin, and renal function tests all remained normal postoperatively. CK was increased to 764 U/l at the time of the first blood gas analysis, peaked at 1189 U/L postoperatively, and declined thereafter [Table 1]. In view of the low CK, myoglobin was not retested. The patient was transferred from the ICU to the ward on the first postoperative day and was discharged home on the second postoperative day.

Consultation with the Malignant Hyperthermia Association of the United States (MHAUS)[1] immediately after the surgery resulted in the recommendation to consider the patient MH susceptible and to send blood for ryanodine receptor gene sequencing to the Department of Pathology, Division of Molecular Diagnostics, at the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA. The report identified a 'heterozygous nucleotide substitution of G to C at nucleotide 742 of exon 9 of the type-1 ryanodine receptor (RYR1)' gene located on chromosome 19q13.1, a change resulting in a 'missense amino acid variant known to cause disease' as per the European Malignant Hyperthermia Group (EMHG).[2] The patient and her family were informed of the genetic test results and the implications to her and her relatives. Over several follow-up calls we recommended that the family members undergo genetic counseling and genetic testing, either through the local department of medical genetics or at an MHAUS center, both of which were informed. MH susceptibility, as well as succinylcholine and all inhalational agents, were added to the patient's electronic medical record in the section on allergies, which will identify her as MH susceptible at any future hospital encounter. To protect her from receiving triggering agents outside this institution and keeping in mind situations where the patient may be unable to provide a history, we also recommended that she wear a medical ID bracelet. The findings, recommendations, and information regarding available resources for MH patients were shared in writing with the patient and her family as well as with the patient's primary care pediatrician.

The patient subsequently underwent a second orthopedic procedure under intravenous anesthesia without problems.

DISCUSSION

Our patient was diagnosed as MH susceptible after postoperative ryanodine receptor gene sequencing identified a mutation causative for MH.[2] Sevoflurane is a known trigger agent for MH, with an incidence for MH of 15 per one million sevoflurane anesthesias in Japan.[3] The intraoperative course of this patient can be suspected

to have been a sevoflurane-triggered MH episode, with hypermetabolism presenting as hypercarbia, modest temperature increase, and mild tachycardia. Although our patient's serum potassium 30 minutes after switching the anesthetic (and with normalized clinical signs) was very high at 7.2 mmol/L – and therefore had perhaps been even higher earlier in the course – there was no other parameter for a muscular pattern of our patient's MH episode (no muscle rigidity, urine discoloration, or myoglobinuria, and only moderate CK increase that was compatible with the original trauma), reflecting only limited rhabdomyolysis.

Larach *et al.* reviewed 286 episodes of MH.[4] Hypercarbia was present in 92.2% and was the most frequent sign of MH. Similarly, in our patient also the persistence of hypercarbia despite doubling the minute ventilation was the concerning sign, with only a moderate increase being noted in temperature and heart rate. Due to the gradual presentation and limited severity of symptoms, we chose to change the anesthetic agent but, being unsure about the diagnosis, decided against the immediate use of dantrolene. The rapid resolution of hyperthermia and hypercarbia with change in ventilation, discontinuation of sevoflurane, and surface cooling alone led us to initially consider MH to be less likely, and at this point we were ambivalent about classifying the patient as MH susceptible. According to the clinical grading scale for MH proposed by Larach *et al.*,[5] the events would have been graded 'somewhat less than likely' to be MH based on clinical signs alone. The blood gas was drawn expecting normal values but with the intention of confirming MH if metabolic changes were present. With documented hyperkalemia, the episode became 'somewhat more than likely' to be MH according to the Larach *et al.* grading scale. The patient was diagnosed as MH susceptible by clinical criteria, ICU admission, MHAUS consultation, and genetic testing were pursued, and patient and family were informed of the MH risk for the patient and relatives.

Our patient was declared MH susceptible based on the clinical course and the metabolic changes seen on blood gas analysis. Genetic testing was pursued on the recommendation of MHAUS[1] since there was no local center for contracture testing, which remains the gold standard to diagnose MH susceptibility.[6] Genetic testing is cheaper than contracture testing and can be performed from a blood sample mailed to the testing institution. An increasing number of ryanodine receptor mutations have been declared causative for MH.[2] The absence of a known mutation causative for MH does not rule out MH and such a report would not have changed our patient's MH susceptible status. However, the finding of a known mutation would allow family members to be tested for the same mutation and be declared MH susceptible if results were positive. However, contracture testing would still be recommended for the patient and for relatives even if the genetic test did not find a causative mutation.[6]

In our case, there was clinical resolution of mild MH symptoms with discontinuation of sevoflurane, hyperventilation, and cooling. Similar resolution of MH signs and symptoms without administration of dantrolene has been reported before.[3,7] It is tempting to use this course as justification for a 'wait-and-see' approach to MH. However, hyperkalemia at the time of clinical normalization demonstrates the potential severity of changes at a cellular level and indicates that this case is more 'near miss' than judicious management. It underlines the importance of following the established guidelines put forward by the various national organizations (MHAUS[1] and EMHG[8]) for acute clinical diagnosis and management. Published guidelines[9] recommend all of the following: Call for help and for dantrolene; immediate discontinuation of the suspected triggering agent and removal of the vaporizer; increase in fresh gas flow and hyperventilation with 100% oxygen; active cooling; discontinuation of surgery if possible; symptomatic treatment of hyperthermia, hyperkalemia, and acidosis; induction of diuresis and, most importantly, administration of dantrolene. Blood gas analysis should be performed early on to look for mixed respiratory and metabolic acidosis. In this case, we did consider MH and follow some of the recommended steps, but we were in disbelief and did not want to call the episode MH until metabolic changes could be documented. This case therefore serves as a reminder to unquestioningly follow the recommended diagnostic and therapeutic algorithms as soon as clinical signs of MH present in the absence of other explanations. Although Larach *et al.*'s series reports a number of patients who were not treated with dantrolene, the recommendation remains very clear that dantrolene should be given if MH is suspected.[4]

In summary, we present the anesthetic course of a 13-year-old girl who, under sevoflurane anesthesia, developed signs of MH, which was subsequently confirmed by genetic sequencing. Discontinuation and symptomatic management alone resulted in resolution of the MH changes without the administration of dantrolene. However, the confirmation of severe hyperkalemia in the presence of mild symptoms in this patient and the final genetic diagnosis of MH susceptibility serve as a reminder that, in the absence of any other explanation, even mild symptoms suggestive of MH should trigger management according to standard MH protocols, which includes early treatment with dantrolene.

REFERENCES

1. Malignant Hyperthermia Association of the United States, Available from: http://www.mhaus.org/ [Last accessed on 2011 March 27].
2. Urwyler A, Deufel T, McCarthy T, West S. European malignant hyperthermia group. Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia. Br J Anaesth 2001;86:283-7.
3. Sumitani M, Uchida K, Yasunaga H, Horiguchi H, Kusakabe Y, Matsuda S, *et al*. Prevalence of malignant hyperthermia and relationship with anesthetics in Japan. Anesthesiology 2011;114:84-90.
4. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. Anesth Analg 2010;110:498-507.
5. Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, *et al*. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 1994;80:771-9.
6. Litman RS, Rosenberg H. Malignant hyperthermia. Update on susceptibility testing. JAMA 2005;293:2918-24.
7. Bonciu M, de la Chapelle A, Delpech H, Depret T, Krivosic-Horber R, Aimé MR. Minor increase of end-tidal CO_2 during sevoflurane-induced malignant hyperthermia. Pediatr Anesth 2007;17:180-2.
8. European Malignant Hyperthermia Group. Available from: Http://www.emhg.org [Last accessed on 2011 March 27].
9. Glahn KP, Ellis FR, Halsall PJ, Müller CR, Snoeck MM, Urwyler A, *et al*. Recognizing and managing a malignant hyperthermia crisis: Guidelines from the European Malignant Hyperthermia Group. Br J Anaesth 2010;105:417-20.