J Vet Intern Med 2005;19:363–367

Malignant Hyperthermia in a Horse Anesthetized with Halothane

Monica Aleman, Robert J. Brosnan, D. Colette Williams, Richard A. LeCouteur, Ayako Imai, Barry R. Tharp, and Eugene P. Steffey

A healthy, 565-kg, 14-year-old Quarter Horse gelding, negative for equine protozoal myelitis on serum Western blot and for hyperkalemic periodic paralysis (HYPP) by polymerase chain reaction, was selected for use in an electrophysiology study performed under inhalation anesthesia. The study was performed by following the guidelines of an Animal Use and Care Committee Protocol of the University of California at Davis (UCD 8578). Anesthesia was induced with halothane delivered via a facemask.[1] The horse was intubated 17 minutes later with an orotracheal tube and anesthesia was maintained with halothane by using a semiclosed, large-animal breathing circuit. Although muscle relaxation was otherwise good, the horse's ears remained tensed in a caudal direction throughout the study.

The horse was placed in left lateral recumbency and allowed to spontaneously ventilate during instrumentation at an end-tidal halothane concentration of approximately 1.1–1.5%. An electroencephalogram (EEG), electro-oculogram (EOG), electromyography (EMG) of the splenius muscle, and respiration monitoring were performed. A total of 16 surface electrodes were fixed on the scalp to record the EEG. The recording montage was a series of bipolar derivations oriented in both a rostral-caudal and transverse fashion. Recordings were produced on a digital EEG system[a] equipped with synchronized video monitoring. An ECG was recorded from a single base-apex lead. Air pressure, arterial blood gases (partial pressure of oxygen [Pa_{O_2}] and partial pressure of carbon dioxide [Pa_{CO_2}]) and pH (pH_a), and jugular venous blood gases (Pv_{O_2} and Pv_{CO_2}) and pH (pH_v) were measured, with values corrected to standard curves derived from tonometry of horse blood with certified gas mixtures. End-tidal partial pressures of CO_2 ($P_{ET}CO_2$) and halothane (P_{ET}HALO), and fraction of inspired oxygen also were measured. All gas volumes were corrected to body temperature by using Charles law. Body temperature was measured by using a nasopharyngeal temperature probe.[b]

The horse was mechanically ventilated to 21.8 cm H_2O peak inspiratory pressure and 0.9 cm H_2O end expiratory pressure at 9.3 breaths/min. P_{ET}HALO was 1.12%, corresponding to 1.2 times the minimum alveolar concentration (MAC) in this species.[1] The initial EEG background activity consisted of an admixture of moderate-amplitude slow activity in the 3- to 6-Hz range (delta and theta) with intermittent frontally dominant 20- to 25-Hz activity. The slow activity often assumed a rhythmic morphology. The frontal beta activity often occurred in spindles. In the early phases of the recording, diphasic and triphasic sharp waves appeared in the frontal and frontal parasagittal regions. After 30 minutes of constant conditions, the horse was allowed to spontaneously ventilate for an additional 15 minutes at the same constant halothane dose.

As part of the research protocol, the peroneal nerve was stimulated with percutaneous electrodes at a frequency of 1 Hz for 10 seconds followed by a single 5.5 seconds of tetanic stimulation at 50 Hz. At that time, the $P_{ET}CO_2$ and temperature remained constant (Fig 1). On EEG, no response was noted with peroneal nerve stimulation at 1 Hz but stimulation at 50 Hz induced a drop in EEG amplitude, increase in frequency, and nystagmus (Fig 2). The halothane dose was changed to 1.6 times the MAC, and mechanical ventilation was resumed. Fourteen minutes later, the EEG background activity was similar to that described for the initial part of the recording (Fig 3). The EOG tracing recorded from the right eye was heavily laden with muscle artifact for the duration of the recording, whereas the splenius muscle EMG electrodes recorded only ECG activity. Approximately 25 minutes after nerve stimulation, there was a 0.7°C rise in body temperature that accompanied a rise in $P_{ET}CO_2$ of 27 mm Hg (Fig 1), despite constant ventilator settings and negligible inspired CO_2. The anesthesia circuit became painfully hot to the touch, and there was a visible increase in the rate of soda lime consumption. Prominent delta activity and waning of frontal beta were observed (Fig 4). During the last 16 minutes of anesthesia, body temperature increased at an average rate of 0.12°C/min and Pa_{CO_2} increased at 3.4 mm Hg/min even though minute ventilation was increased 40% during this time. The Pa_{O_2} decreased from 282 to 122 mm Hg because of progressive venous admixture, Pv_{O_2} at the end of anesthesia was 27 mm Hg, and Pa_{CO_2} increased from 69 to 274 mm Hg. The base excess decreased 4.2 mmol/L; this change along with the rise in Pa_{CO_2} caused pH_a to decrease from 7.26 to 6.72. During the last 7 minutes of anesthesia, minute ventilation could not be further increased because of time-constant limitations imposed by the Bird ventilator, bag-in-barrel anesthetic circuit thus allowing an unabated final rise in $P_{ET}CO_2$ (Fig 1). At that time, numerous generalized sharp events, triphasiclike waves, were noted on EEG (Fig 5). These events were maximal in the frontal region.

A clinical diagnosis of malignant hyperthermia was made based on rapid, progressive, and severe hyperthermia, hypercapnea, and acidosis; therefore, the horse was disconnected from the anesthetic circuit. Efforts directed at patient

From the Department of Veterinary Surgical and Radiological Sciences (Aleman, Brosnan, Williams, LeCouteur, Imai, Steffey), and the MIND Institute (Tharp), University of California, Davis, Medical Center, Davis, CA. *Previously presented as an abstract at the Association of Veterinary Anaesthetists, Dunblane, Scotland, September 2001, with abstract published (Vet Anaesth Analg 2002;29:91).*

Reprint requests: Monica Aleman, MVZ, PhD, Dip ACVIM, Department of Veterinary Surgical and Radiological Sciences, Tupper Hall 2112, One Shields Avenue, University of California, Davis, Davis, CA 95616; e-mail: mraleman@ucdavis.edu.

Submitted September 28, 2004; Revised November 30, 2004; Accepted January 20, 2005.

0891-6640/05/1903-0012/$3.00/0

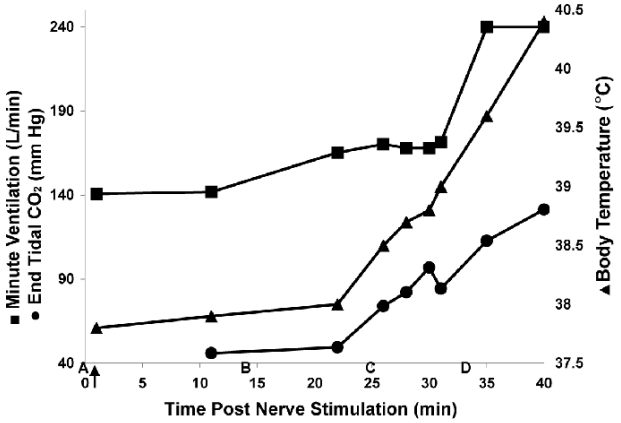

Fig 1. Minute ventilation (squares), end-tidal CO_2 (circles), and body temperature (triangles) versus time after electrical stimulation in a mechanically ventilated horse anesthetized with halothane at 1.2 times the minimum alveolar concentration (MAC) at time 0, and 1.6 times the MAC at time 1.5 minutes (arrow) and for the remaining duration of the study. Letters correspond to serial electroencephalogram figures.

cooling including ice packs over whole body, cold water, alcohol, intravenous fluids, and application of fans were ineffective. Injectable dantrolene was not available. Breathing was supported with a Hudson oxygen-demand valve placed over the endotracheal tube. The ECG showed an irregular tachycardia. The last minute of the EEG recording contained low-frequency activity (0.3–0.5 Hz) thought to be an artifact induced by sweat (Fig 6). The horse was transferred to a recovery stall where it soon developed cardiopulmonary arrest and died. Profound rigor mortis was present almost immediately.

The important laboratory findings of blood samples collected 2 minutes before death were a PCV of 58% (reference range, 32–52%), plasma protein of 7.9 g/dL (reference range, 5.8–7.7 g/dL), clumped platelets, sodium of 156 mmol/L (reference range, 132–140 mmol/L), potassium of

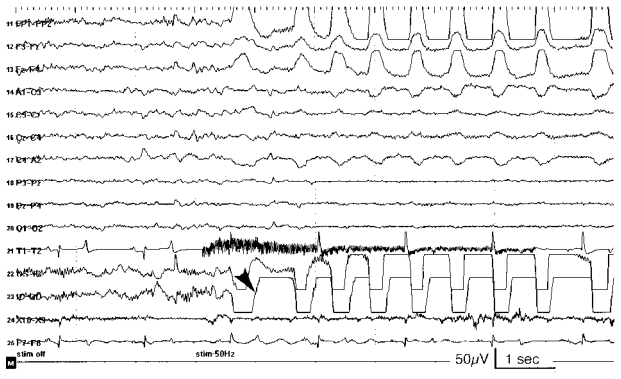

Fig 2. Electroencephalogram (EEG) under halothane anesthesia is displayed with a bipolar, transverse montage. Channels 11–20 are EEG, 21 is ECG, 22 is left-eye electro-oculogram (EOG), 23 is right eye EOG, 24 is respiration, and 25 is electromyogram. For the duration of the EEG study, the time-constant and high-frequency filter were set at 0.1 and 35 Hz, respectively. Time 0 on the previous figure corresponds to the onset of 50-Hz stimulation, which is represented by the artifact in the ECG channel. High-amplitude slow waves are eye movement artifacts due to nystagmus (arrowhead).

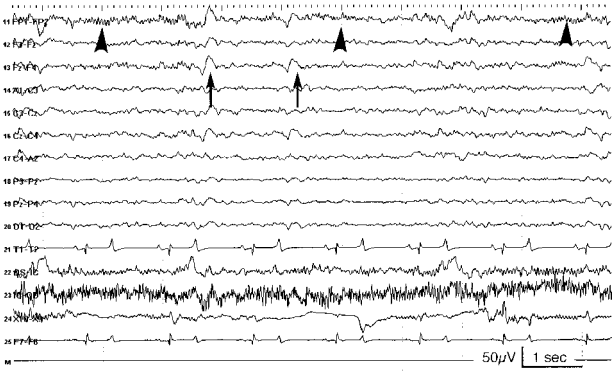

Fig 3. Electroencephalogram shows beta activity (arrowheads) and periodic slow waves (arrows).

6.6 mmol/L (reference range, 2.6–4.8 mmol/L), calcium of 15.6 mg/dL (reference range, 11.0–13.1 mg/dL), phosphorus of 11.5 mg/dL (reference range, 2.1–4.7 mg/dL), creatinine of 3.1 mg/dL (reference range, 0.9–2.0 mg/dL), blood urea nitrogen of 29 mg/dL (reference range, 12–27 mg/dL), glucose of 193 mg/dL (reference range, 59–122 mg/dL), creatine kinase activity of 843 U/L (reference range, 119–287 U/L), and myoglobin of 98.4 ng/mL (reference range, 0–9 ng/mL).

Postmortem examination findings included hyperplastic adrenal glands as the result of cortical hyperplasia within the zona fascicularis, moderate multifocal renal arteriosclerosis suggestive of a hypertensive state, and mild diffuse acute congestion of the brain, which could be responsible for an increase of intracranial pressure. Multiple skeletal muscles were evaluated. The histologic findings were mild to moderate multifocal acute myolysis, interfascicular edema, and hypercontraction. These changes were more pronounced in the diaphragm. The muscle histologic findings were bilaterally symmetrical.

Malignant hyperthermia is a pharmacogenetic disease triggered by inhalation anesthesia, depolarizing muscle relaxants, and stress.[2] A genetic basis linked to mutations in the ryanodine receptor 1 (*RyR1*) gene is confirmed in humans, pigs, and dogs.[3–5] The role of *RyR1* in skeletal muscle excitation-contraction coupling is essential. The disease has been suspected in horses since 1975, but limited information is available, as evidenced by few reports.[6–15] The dis-

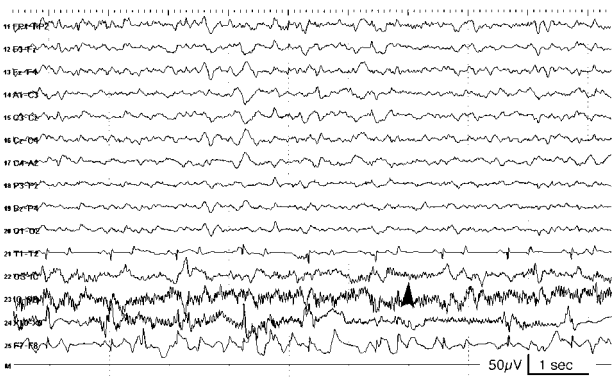

Fig 4. Electroencephalogram depicts the diminished beta activity (arrowhead), which disappears shortly thereafter.

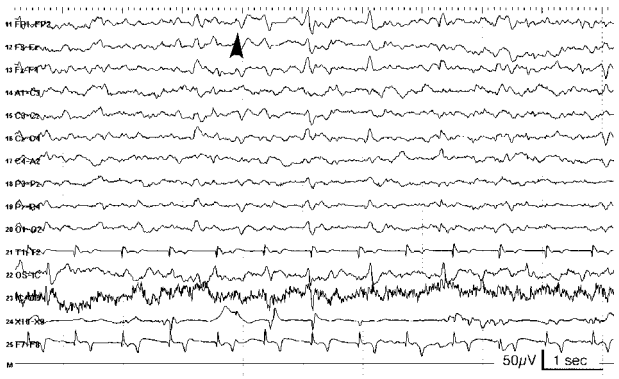

Fig 5. Electroencephalogram demonstrates numerous triphasiclike waves (arrowhead). Tachycardia is evident.

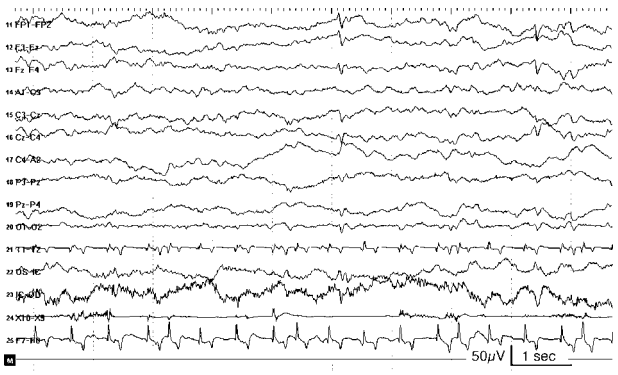

Fig 6. Electroencephalogram (EEG) shows a low-frequency pattern that is evidenced by fluctuating baselines. Note the irregular tachycardia. This EEG segment was recorded shortly before death.

ease is reported in Quarter Horses, Thoroughbreds, Appaloosas, Arabs, and ponies. No sex or age predisposition is identified.[6–15] This report describes an extensively monitored case of malignant hyperthermia, and represents 1 of 2 horses in which a C7360G mutation in *RyR1* exon 46 generated a R2454G substitution.[16] In humans, C7360T and G7361A nucleotide mutations generate R2454C and R2454H amino acid substitutions.[17] These mutations confer susceptibility to malignant hyperthermia in humans. The nucleotide and amino acid sequences in that region are conserved across several species.

The most common clinical signs in horses suspected to have malignant hyperthermia triggered by halothane alone, halothane with succinylcholine, and halothane with nerve stimulation were hyperthermia (39 to >42°C), profuse sweating, tachycardia, tachypnea, and muscle rigidity.[6–15] Reported laboratory abnormalities included hypercapnea, acidosis, hypertension, electrolyte disorders, and increased serum creatine kinase activity. These clinical and laboratory abnormalities were observed in the horse of this report and are comparable to those described in humans and pigs.[2] Dogs appear to have milder malignant hyperthermia episodes in which profound muscle rigidity is not typically observed but fatalities occur.[5] Although the overall mortality in horses associated with halothane anesthesia was reported to be 1.5% by Johnston et al,[18] the mortality associated with malignant hyperthermia–like episodes was 31%. An additional case, a 12-day-old Quarter Horse filly with suspected HYPP that was anesthetized several times with isoflurane developed mild hypercapnea, hyperthermia, and increase of muscle enzymes, but lacked other signs consistent with malignant hyperthermia.[19] Human cases of HYPP and hypokalemic periodic paralysis associated with malignant hyperthermia are rarely reported.[20,21]

This report describes the EEG findings in a horse with confirmed malignant hyperthermia triggered by halothane. Some of the EEG events throughout the study in this horse may have been influenced by the variable states of consciousness. However, other features such as the beta activity observed in the horse of this report have been reported in malignant hyperthermia–susceptible pigs anesthetized with halothane.[22] In addition, the triphasiclike waves were thought to be associated with various metabolic derangements as the result of the developing and ongoing malignant hyperthermia episode.[23]

Genotypically, the horse of the present report was found to be heterozygous for the C7360G mutation, but presented a malignant hyperthermia phenotype when challenged with halothane and nerve stimulation, suggesting a dominant susceptibility. It is unknown if equine malignant hyperthermia is an inherited disease as in humans, pigs, and dogs. In addition, it is unknown if the mutation described in the horse of this report is responsible for all cases of equine malignant hyperthermia. Early recognition of an episode with immediate discontinuation of inhalation anesthesia or depolarizing muscle relaxants, and administration of body-cooling therapy and dantrolene are measures aimed at preventing fatalities. Further studies are needed to gain insight into the pathophysiology and management of equine malignant hyperthermia, but identification of susceptible individuals is essential in order to study the disease. However, this could represent a challenge because the disease manifests in the presence of triggering events. Genetic screening of susceptible horses recognized during a malignant hyperthermia episode, screening of their relatives, and pedigree and population analyses are the initial steps for future studies that will help to elucidate the prevalence and disease process in the horse.

Footnotes

[a] EEG-2110, Nihon Kohden Corp, Irvine, CA

[b] Nasopharyngeal temperature probe, Yellow Springs Instrument Co, Yellow Springs, OH

References

1. Steffey EP, Howland D Jr. Comparison of circulatory and respiratory effects of isoflurane and halothane anesthesia in horses. Am J Vet Res 1980;41:821–825.

2. Denborough M. Malignant hyperthermia. Lancet 1998;352: 1131–1136.

3. McCarthy TV, Healy JM, Heffron JJ, et al. Localization of the malignant hyperthermia susceptibility locus to human chromosome 19q12-13.2. Nature 1990;343:562–564.

4. Fujii J, Otsu K, Zorzato F, et al. Identification of a mutation in

porcine ryanodine receptor associated with malignant hyperthermia. Science 1991;253:448–451.

5. Roberts MC, Mickelson JR, Patterson EE, et al. Autosomal dominant canine malignant hyperthermia is caused by a mutation in the gene encoding the skeletal muscle calcium release channel (*RYR1*). Anesthesiology 2001;95:716–725.

6. Hildebrand SV, Howitt GA. Succinylcholine infusion associated with hyperthermia in ponies anesthetized with halothane. Am J Vet Res 1983;44:2280–2284.

7. Hildebrand SV, Arpin D, Howitt GA, et al. Muscle biopsy to differentiate normal from suspected malignant hyperthermia horses and ponies. Vet Surg 1988;17:172–173.

8. Hildebrand SV, Arpin D, Cardinet G III. Contracture test and histologic and histochemical analyses of muscle biopsy specimens from horses with exertional rhabdomyolysis. J Am Vet Med Assoc 1990;196:1077–1083.

9. Klein LV. A hot horse. Vet Anesth 1975;2:41–42.

10. Manley SV, Kelly AB, Hodgson D. Malignant hyperthermia–like reactions in three anesthetized horses. J Am Vet Med Assoc 1983; 183:85–89.

11. Riedesel DH, Hildebrand SV. Unusual response following use of succinylcholine in a horse anesthetized with halothane. J Am Vet Med Assoc 1985;187:507–508.

12. Waldron-Mease E, Rosenberg H. Post anesthetic myositis in the horse associated with in vitro malignant hyperthermia susceptibility. Vet Sci Commun 1979;3:45–50.

13. Waldron-Mease E, Klein LV, Rosenberg H, et al. Malignant hyperthermia in a halothane-anesthetized horse. J Am Vet Med Assoc 1981;179:896–898.

14. Smyth GB. Spinal cord decompression and stabilization of a comminuted axis fracture complicated by intraoperative malignant hyperthermia like reaction in a filly. Aust Equine Vet 1992;10:133–136.

15. Klein L, Ailes N, Fackelman GE, et al. Postanesthetic equine myopathy suggestive of malignant hyperthermia. A case report. Vet Surg 1989;18:479–482.

16. Aleman M, Riehl J, Aldridge BM, et al. Association of a mutation in the ryanodine receptor 1 gene with equine malignant hyperthermia. Muscle Nerve 2004;30:356–365.

17. Brandt A, Schleithoff L, Jurkat-Rott K, et al. Screening of the ryanodine receptor gene in 105 malignant hyperthermia families: Novel mutations and concordance with the in vitro contracture test. Hum Mol Genet 1999;8:2055–2062.

18. Johnston GM, Eastment JK, Taylor PM, et al. Is isoflurane safer than halothane in equine anaesthesia? Results from a prospective multicentre randomised controlled trial. Equine Vet J 2004;36:64–71.

19. Cornick JL, Seahorn TL, Hartsfield SM. Hyperthermia during isoflurane anaesthesia in a horse with suspected hyperkalemic periodic paralysis. Equine Vet J 1994;26:511–514.

20. Moslehi R, Langlois S, Yam I, et al. Linkage of malignant hyperthermia and hyperkalemic periodic paralysis to the adult skeletal muscle sodium channel (*SCN4A*) gene in a large pedigree. Am J Med Genet 1998;76:21–27.

21. Rajabally YA, El Lahawi M. Hypokalemic periodic paralysis associated with malignant hyperthermia. Muscle Nerve 2002;25:453–455.

22. Kochs E, Hoffman WE, Roewer N, et al. Alterations in brain electrical activity may indicate the onset of malignant hyperthermia in swine. Anesthesiology 1990;73:1236–1242.

23. Chatrian GE, Turella GS. Electrophysiological evaluation of coma, other states of diminished responsiveness and brain death. In: Ebersole JS, Pedley TA, eds. Current Practice of Clinical Electroencephalography, 3rd ed. Philadelphia, PA: Lippicott, Williams & Wilkins; 2003:405–462.