Dantrolene sodium is a lipophilic hydantoin derivative used to treat or prevent various neuromuscular disorders in humans and animals.1–3 The efficacy of dantrolene for treatment of central neurodegenerative disorders has also been explored.4,5 Despite the widespread use of dantrolene for the treatment of a variety of human and animal disorders and despite extensive investigation, dantrolene’s exact mechanism of action is not clearly understood, but is likely multifaceted and involves suppression of calcium release from the sarcoplasmic and endoplasmic reticula and modification of calcium entry into cells.1,6–10 Regardless of its mechanism of action, one of the primary effects of dantrolene is the inhibition of calcium efflux from these receptors, specifically the RyR1 isoform in skeletal muscle and the RyR3 isoform in neural tissue, with minimal impact on the RyR2 isoform in healthy cardiac muscle.1,8–10

In veterinary medicine, dantrolene is typically recognized for its efficacy in the prevention and treatment of malignant hyperthermia in susceptible dogs3 and pigs.11 The pharmacokinetics of dantrolene has been established for horses,12,13 and dantrolene has been used for the treatment or prevention of anesthetic myopathy and exertional rhabdomyolysis in horses.2,14 In a crossover study4 that involved the induction of hypotensive anesthetic myopathy in 7 healthy horses, administration of dantrolene sodium (6 mg/kg, PO) prior to 90 minutes of anesthesia maintained with isoflurane resulted in an increase in serum CK activity, compared with that when horses were administered only water prior to anesthesia. Also during that study,4 the CO as measured by a lithium-

Effect of dantrolene premedication on various cardiovascular and biochemical variables and the recovery in healthy isoflurane-anesthetized horses

OBJECTIVE
To determine the effect of dantrolene premedication on various cardiovascular and biochemical variables and recovery in isoflurane-anesthetized horses.

ANIMALS
6 healthy horses.

PROCEDURES
Each horse was anesthetized twice with a 21- to 28-day washout period between anesthetic sessions. Food was not withheld from horses before either session. During each session, dantrolene (6 mg/kg in 2 L of water) or water (2 L) was administered via a nasogastric tube 1 hour before anesthesia was induced. Anesthesia was maintained with isoflurane for 90 minutes, during which blood gas analyses and lithium-dilution cardiac output (CO) measurements were obtained every 10 minutes. Serum creatine kinase activity was measured before and at 4, 8, and 12 hours after anesthesia.

RESULTS
When horses were premedicated with dantrolene, CO at 25, 35, and 45 minutes after induction of anesthesia was significantly lower than that when horses were premedicated with water after which time difficulty in obtaining valid measurements suggested a continued decrease in CO; plasma potassium concentration progressively increased during anesthesia, whereas serum creatine kinase activity remained fairly stable and within reference limits through 12 hours after anesthesia; and 2 of 6 horses developed cardiac arrhythmias that required medical intervention. The quality of anesthetic recovery was slightly better when horses were premedicated with dantrolene versus water, although the time required for recovery did not differ significantly between treatments.

CONCLUSIONS AND CLINICAL RELEVANCE
Results suggested that dantrolene premedication prevented muscle damage without affecting anesthetic recovery but impaired CO and precipitated hyperkalemia and cardiac arrhythmias in healthy isoflurane-anesthetized horses. (Am J Vet Res 2015;76:293–301)

ABBREVIATIONS
CK Creatine kinase
CO Cardiac output
P ET CO 2 End-tidal partial pressure of carbon dioxide
RyR Ryanodine receptor
The dilution technique at 60 minutes into anesthesia was significantly lower than the CO measured at 15 minutes into anesthesia when horses were premedicated with dantrolene but not when they were premedicated with water; however, no clinically relevant effects associated with that decrease in CO were observed.

Administration of dantrolene prior to or during anesthesia is associated with other adverse effects including hyperkalemia in dogs, pigs, and humans, and prolonged recumbency after anesthesia was reported in a draft horse that was premedicated with a high dose of dantrolene (9 mg/kg, PO). Although hyperkalemia following premedication with dantrolene has frequently been attributed to the concurrent administration of calcium channel blocking agents or malignant hyperthermia, the role of dantrolene in the development of hyperkalemia is unclear. Collectively, the findings of those studies suggest that administration of dantrolene to human and veterinary patients prior to anesthesia may be associated with several adverse effects.

The objective of the study reported here was to determine the effect of premedication with dantrolene on various cardiovascular and biochemical variables in healthy isoflurane-anesthetized horses including CO, serum CK activity, plasma potassium concentration, and the duration and quality of recovery from anesthesia. We hypothesized that premedication of horses from which food had not been withheld with dantrolene (6 mg/kg, nasogastrically) 60 minutes prior to anesthesia would result in measureable decreases in CO and mitigate the anesthesia-induced increase in serum CK activity from baseline values.

**Materials and Methods**

**Animals**

Six healthy adult horses were used in the study and included 3 mares, 2 geldings, and 1 stallion that ranged from 8 to 25 years old. Breeds represented included Quarter Horse (negative for hyperkalemic periodic paralysis; n = 2), Thoroughbred (2), Tennessee Walking Horse (1), and warmblood (1). All study procedures were reviewed and approved by the Oregon State University Institutional Animal Care and Use Committee.

**Experimental design**

The study had a randomized crossover design. All horses were randomly assigned to be premedicated with dantrolene sodium (6 mg/kg dissolved in 2 L water) or water (2 L) via nasogastric intubation 1 hour before the first anesthetic session and then were administered the opposite premedication 1 hour before the second anesthetic session 21 to 28 days later.

**Treatment administration and anesthetic procedures and instrumentation**

During the 24 hours prior to each anesthetic session, each horse was individually confined in a stall with ad libitum access to fresh water and grass hay. A 14-gauge, 5.5-inch catheter was aseptically placed in a jugular vein, secured to the skin with sutures, and flushed with 10 mL of heparinized saline (NaCl) solution every 6 hours. Horses had access to hay until the time of anesthesia induction to avoid the negative effect that the withholding of food can have on the absorption of enterally administered dantrolene in this species.

Prior to administration of the assigned premedication, each horse was sedated with xylazine (0.3 mg/kg, IV) to facilitate nasogastric intubation. Sixty minutes later, each horse received an additional dose of xylazine (1.1 mg/kg, IV), and anesthesia was induced with ketamine (2.2 mg/kg, IV). Horses were positioned in lateral recumbency on the floor of an induction stall and intubated with an endotracheal tube. Anesthesia was maintained by inhalation of isoflurane in 100% oxygen for 90 minutes. Respiration was mechanically controlled with a volume-controlled ventilator at a rate of 6 breaths/min with an inspiration-to-expiration ratio of 1:2 and a target peak inspiratory pressure of 20 cm H2O. Ventilator and vaporizer settings were adjusted as necessary to maintain the PETCO2 between 34 and 36 mm Hg and the end-tidal concentration of isoflurane between 1.3% and 1.5%, values consistent with the minimum alveolar concentration of isoflurane reported for horses. Depth of anesthesia was determined by periodic assessment of ocular movement and evoked palpebral reflexes. The tidal volume setting varied between 13 and 18 mL/kg. Lactated Ringer’s solution (10 mL/kg/h, IV) was infused through the jugular catheter throughout anesthesia. Lubricating eye ointment was topically applied to each eye, and the horse’s head was placed on a soft flat pad. The dependent forelimb was pulled forward, and a semi-inflated inner tube was positioned under the shoulder. The nondependent limbs were mechanically supported in a horizontal position parallel to the floor.

A multiparameter monitor was used to obtain pulse oximetry, 3-lead ECG, side-stream capnography, and inhaled and exhaled gas analysis data. Arterial blood pressure was measured directly through an 18-gauge, 1-inch catheter that was placed in the nondependent facial artery and connected to an electronic pressure transducer with an extension line filled with heparinized saline solution. The pressure transducer was positioned at the level of the base of the heart and secured to the skin at the thoracic inlet with a clip. Atmospheric pressure was used as the zero reference point. The transducer was then connected to the multiparameter monitor, where the blood pressure measurements were displayed. Data obtained from the multiparameter monitor were manually recorded every 5 minutes throughout the duration of anesthesia.

Isoflurane administration and mechanical ventilation were discontinued after 90 minutes. The endotracheal tube was left in place and secured to the horse’s head with adhesive tape. Manual ventilation was provided at a rate of 3 breaths/min until spontaneous ven-
tilation resumed, after which 100% oxygen was administered through the endotracheal tube at a rate of 10 L/min until the horse was standing.

After spontaneous ventilation resumed, each horse was allowed to recover autonomously and spontaneously within the induction stall. Video cameras mounted on the wall of the induction stall recorded each horse’s recovery until it achieved a standing position, at which time recording was stopped and the endotracheal tube was removed, marking the end of the anesthetic session.

Each horse was anesthetized for a second time 21 to 28 days after the first anesthetic session. The procedures for the second anesthetic session were the same as those for the first session, except each horse received the opposite treatment (dantrolene or water) and was positioned in lateral recumbency on the opposite side to minimize cumulative trauma to dependent musculature.

**CO measurement**

Cardiac output was measured by means of a lithium-dilution method that used a commercially available disposable lithium-ion selective sensor and CO monitor as described for adult horses. Briefly, an 18-gauge, 1.5-inch catheter was placed in the dorsal metatarsal artery of the nondependent hind limb and connected to the lithium sensor, which was operated after administration of 20 mL of lithium chloride solution (0.15 mmol/mL) through the catheter in the jugular vein. The lithium chloride solution was compounded in our laboratory, and a benchtop blood gas analyzer was used to verify that the chloride concentration of the solution was between 150 and 156 mEq/L. Cardiac output was measured every 10 minutes during each anesthesia session beginning 15 minutes after initiation of isoflurane administration; thus, CO was measured 7 times (annotated as T1 to T7) during each anesthetic session.

**Sample collection and analysis**

Blood samples (6 mL each) were obtained from the catheter in the jugular vein immediately prior to dantrolene administration and at 4, 8, and 12 hours after discontinuation of isoflurane administration to obtain serum for measurement of potassium concentration (only in the sample obtained immediately prior to dantrolene administration) and CK activity (all samples). Additional blood samples (6 mL each) were collected into sterile tubes that contained EDTA at 10-minute intervals from 40 to 150 minutes after dantrolene administration to obtain plasma for measurement of dantrolene concentration by means of high-performance liquid chromatography. Blood samples (2 mL each) were collected into lightly heparinized syringes from the catheter in the dorsal metatarsal artery immediately before each CO calculation for arterial blood gas analysis, which was performed with a benchtop blood gas analyzer. Variables of interest extracted from the blood gas results for analysis included plasma pH and potassium, sodium, bicarbonate, and ionized calcium concentrations.

Hair samples (approximately 30 hairs including the root) were obtained from the mane of each horse and analyzed by a PCR assay for the R309H mutation in the glycogen synthase 1 gene that causes type 1 polysaccharide storage myopathy and the C7560G mutation in the RyR1 gene that causes malignant hyperthermia.

**Data analysis**

For each horse, the videos of its recovery from each anesthetic session were collated and retrospectively evaluated separately by 2 board-certified veterinary anesthesiologists, who were unaware of the treatment assigned to each horse during a given session. Recovery quality for each anesthesia session was evaluated by use of a modified version of a previously reported scoring system. Briefly, each investigator evaluated several variables, including the horse’s demeanor, strength, coordination, and the number and quality of attempts to stand, and assigned each a subjective score. The cumulative score for recovery from each anesthetic session could range from 8 (ideal recovery) to 31 (disastrous recovery).

The lithium dilution curves used to calculate the CO measurements were submitted to an engineer employed by the manufacturer of the lithium-ion sensor for evaluation. Individual curves with unsuitable quality were identified, and the CO measurements calculated from those curves were not included in the statistical analyses. Cardiac index was calculated as CO per kilogram of body weight as determined on the day of each anesthetic session to account for differences in body weight among horses and within each horse between anesthetic sessions.

Data were analyzed with an ANOVA for repeated measures with an autoregressive period 1 covariance structure. A mixed model was used that included a random variable to account for the crossover study design and missing data points. Results were reported as the mean ± SEM, and values of P < 0.05 were considered significant for all analyses.

**Results**

**Animals**

The mean body weight of the horses was 502 ± 38 kg when premedicated with water and 501 ± 44 kg when premedicated with dantrolene (range for both treatments, 368 to 678 kg). All horses survived the study, although some complications were encountered. When premedicated with dantrolene, 2 horses subsequently developed cardiac arrhythmias while anesthetized. One horse developed a persistent 2:1 atrioventricular block that rapidly progressed to complete heart block with up to 8 consecutive atrial complexes that were unaccompanied by evidence of ventricular excitation approximately 60 minutes into anesthesia. The other horse developed brady-
cardia (heart rate, 15 beats/min) and a sinoventricular rhythm approximately 85 minutes into anesthesia. For both horses, isoflurane administration was discontinued, and atropine (5 mg, IV, once), sodium bicarbonate (0.3 mEq/kg, IV, once), and 50% dextrose solution (0.25 mL/kg, IV, once) were administered. Both horses subsequently recovered from anesthesia with no other apparent complications.

Another horse inhaled the endotracheal tube immediately after achieving a standing position during recovery from anesthesia approximately 3.5 hours after dantrolene administration. The horse was immediately reanesthetized with a combination of xylazine (1.75 mg/kg, IV), ketamine (3 mg/kg, IV), and guaifenesin (200 mL of a 10% solution, IV) to recover the endotracheal tube. The horse remained in lateral recumbency for several hours after anesthesia was discontinued and, on standing, had signs of unilateral myopathy of the left triceps brachii muscle (dependent limb) that included lameness and tissue firmness and swelling. The horse recovered completely after several days of medical management; however, all serum CK activity data for that horse were excluded from the statistical analysis.

### Plasma and serum variables

Plasma pH and bicarbonate and ionized calcium concentrations remained within the respective reference intervals and fluctuated only minimally throughout anesthesia for all horses (data not shown). When horses were premedicated with water, the mean ± SEM plasma pH (7.450 ± 0.008) was significantly (*P* = 0.04) higher than that when horses were premedicated with dantrolene at 15 minutes after anesthesia induction (7.435 ± 0.008; T1), but not at any of the other measurement times (T2 through T7). Similarly, the mean ± SEM plasma bicarbonate concentration (31.5 ± 0.6 mmol/L) when horses were premedicated with water was significantly (*P* = 0.02) higher than that when horses were premedicated with dantrolene (29.8 ± 1.3 mmol/L) at T2, but not at any of the other measurement times. The mean plasma ionized calcium concentrations did not differ significantly between the 2 treatments (ie, premedication with water or dantrolene) at any time during anesthesia.

The mean plasma potassium concentration did not vary significantly during anesthesia when horses were premedicated with water. However, when horses were premedicated with dantrolene, the mean plasma potassium concentration progressively increased during anesthesia and was significantly greater at T6 and T7, compared with that at T4 and T5, which was significantly greater than the mean plasma concentration at T1 through T3 (Figure 1). When premedicated with dantrolene, 4 of 6 horses developed plasma potassium concentrations ≥ 5.5 mEq/L, and 2 of those horses had concentrations ≥ 7.0 mEq/L, whereas only 1 horse developed a plasma potassium concentration > 5.5 mEq/L (ie, 5.6 mEq/L) when premedicated with water. For the 2 horses that developed cardiac arrhythmias during anesthesia following premedication with dantrolene, the respective plasma potassium concentrations were 7.0 and 5.5 mEq/L at the observation immediately before identification of the arrhythmia. For the horse that developed bradycardia 85 minutes after initiation of anesthesia, the plasma potassium concentration increased from 7.0 mEq/L to 7.6 mEq/L immediately prior to medical intervention. The plasma potassium concentrations in both horses with cardiac arrhythmias declined rapidly after medical intervention.

Mean serum CK activity immediately prior to premedication did not differ between the water and dantrolene treatments. Although the mean serum CK activity was greater when horses were premedicated with water than that when they were premedicated with dantrolene at 4, 8, and 12 hours after anesthesia, this difference was not significant at any time (Figure 2). Following premedication with water, 3 of 6 horses developed serum CK activities that were increased from the reference interval (145 to 633 U/L). The serum CK activity peaked at 4,763 U/L 4 hours after anesthesia for one of those horses, at 920 U/L 8 hours after anesthesia for another, and at 13,358 U/L 12 hours after anesthesia for the remaining horse. The peak serum CK activity (668 U/L) for the horse that developed a pathological cardiac arrhythmia 60 minutes after initiation of anesthesia following dantrolene premedication was only slightly above the reference interval at 12 hours after anesthesia was discontinued. Although the serum CK activ-

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**Figure 1**—Mean ± SEM plasma potassium concentrations in 6 healthy adult horses immediately before (pre) administration of water (2 L; white bars) or dantrolene sodium (6 mg/kg dissolved in 2 L of water; gray bars) via a nasogastric tube 60 minutes prior to anesthesia induction and at 10-minute intervals beginning 15 minutes after anesthesia induction (T1). Anesthesia was maintained with isoflurane for 90 minutes. The study had a crossover design, and all horses were anesthetized twice with a 21- to 28-day washout period between anesthetic sessions. Bars and brackets represent the mean ± SEM for 6 horses except as follows: the bars and brackets for the dantrolene treatment represent the mean ± SEM for 5 horses at T5, 4 horses at T6, and 3 horses at T7. *Within the dantrolene treatment only; the values for bars with different superscript letters differ significantly (*P* < 0.05). *Within an observation, values differ significantly (*P* < 0.05) between treatments.
ity for the horse that had to be reanesthetized to recover the endotracheal tube was excluded from all statistical comparisons, it was 1,598 U/L approximately 5 hours after the end of the planned anesthetic session and continued to increase to 10,729 U/L at 12 hours and 26,600 U/L at 24 hours after the planned anesthetic session.

When horses were premedicated with dantrolene, the plasma dantrolene concentration remained fairly consistent throughout anesthesia within individual horses, but it was quite variable among horses (Figure 3). The mean ± SEM plasma dantrolene concentrations over time for 2 of the horses (354 ± 26 ng/mL and 267 ± 13 ng/mL) were substantially lower than those for the other 4 horses (range, 676 ± 40 ng/mL to 936 ± 20 ng/mL).

Cardiovascular variables
Mean systolic and diastolic arterial pressures did not differ significantly between treatments; however, mean arterial pressure when horses were premedicated with dantrolene was significantly lower at T6 and T7, compared with the mean arterial pressure when horses were premedicated with water (Table 1). When horses were premedicated with dantrolene, the systolic and mean arterial pressures were higher at T1, compared with the systolic and mean arterial pressures at all other measurement times. The systolic and mean arterial pressures did not change over time when horses were premedicated with water. The mean heart rates at T4 through T6 were significantly lower, compared with the mean heart rate at T1 when horses were premedicated with dantrolene, whereas the mean heart rate did not vary significantly at any time during anesthesia when horses were premedicated with water.

When horses were premedicated with water, valid lithium dilution curves were obtained at each measurement time for all but 1 horse, for which a valid lithium dilution curve was not obtained at T5 and T7. However, when horses were premedicated with dantrolene, valid lithium dilution curves were obtained from only 5 horses at T1 and T2 and 4 horses at T3 and T4, were not obtained for any of the horses at T5, and were obtained from only 1 horse at T6 and T7. Analysis of the valid data revealed that the mean CO and cardiac index were significantly higher at T2, T3, and T4 when horses were premedicated with water versus dantrolene (Table 1). For the 1 horse for which valid lithium dilution curves were obtained at T6 and T7 when anesthetized following dantrolene premedication, the CO (T6, 23.9 L/min; T7, 19.0 L/min) and cardiac index (T6, 49.6 mL/kg/min; T7, 39.5 mL/kg/min) were substantially lower than the CO (30.4 L/min) and cardiac index (63.1 mL/kg/min) at T1.

Anesthetic variables
Mean ± SEM end-tidal concentration of isoflurane during anesthesia ranged from 1.48 ± 0.07% to 1.55 ± 0.03% and did not differ significantly between treatments. Mean ± SEM PetCO₂ ranged from 33.0 ± 1.0 mm Hg to 37.2 ± 1.5 mm Hg and did not differ significantly between treatments at any time except T7, when the mean ± SEM PetCO₂ when horses were premedicated with water (35.5 ± 1.3 mm Hg) was significantly greater than that when horses were premedicated with dantrolene (33.0 ± 1.0 mm Hg).
The study had a randomized crossover design, and each horse was anesthetized twice with a 21- to 28-day washout period between anesthetic sessions. Beginning 15 minutes after initiation of isoflurane administration, cardiac variables were measured every 10 minutes until isoflurane was discontinued. Thus, T1 corresponds to the first observation obtained 15 minutes after initiation of isoflurane administration, and T7 corresponds to the last observation obtained approximately 75 minutes after initiation of isoflurane administration. Some CO measurements failed to meet the validity criteria for analysis and were discarded along with the corresponding cardiac index measurements. Therefore, the values for CO and cardiac index were not acquired in 10 horses from which food had not been withheld with dantrolene and in 2 of the horses for the water premedication at T5 and T7. When dantrolene was administered, valid measurements for CO were not acquired for any of the horses at T5 and were acquired for only 1 horse at T6 and T7.

Within a variable, the value for the water premedication differs significantly (P < 0.05) from that for the dantrolene premedication. †Represents the value for only 1 horse.

aWithin a row, values with different superscripts differ significantly (P < 0.05).
over, the peak blood dantrolene concentration for the horses of the present study was 2 to 3 times that for horses from which food was withheld for 12 hours and that received the same dose of dantrolene as the one administered in the present study and 5 to 25 times that for horses from which food was withheld for 12 hours and that received 1 mg/kg, PO, or 4 mg/kg, nasogastrically. Collectively, these results suggest that prolonged withholding of food prior to dantrolene administration substantially reduces gastrointestinal absorption of dantrolene in horses. Results of another study suggest that the withholding of food may similarly reduce the bioavailability of dantrolene following oral administration in dogs. However, withholding of food from patients for a prescribed period is traditionally considered desirable before elective procedures that require anesthesia and complicates the use of dantrolene as a premedication for horses and dogs. Furthermore, the marked variation in the peak plasma dantrolene concentration observed among individuals that received the same dose of the drug in the present study and other studies makes it challenging to determine a dose that will achieve predictable blood dantrolene concentrations. Because plasma dantrolene concentrations vary substantially with the dose administered and the patient’s access to food, the establishment of recommendations for the appropriate drug withdrawal period for horses treated with dantrolene to control exertional rhabdomyolysis during training is difficult.

To our knowledge, a therapeutic plasma concentration for dantrolene has not been established for horses, and it is possible that plasma dantrolene concentrations substantially lower than those observed in the present study could effectively prevent muscle injury and be less likely to induce adverse effects.

In the horses of the present study, dantrolene administration resulted in a progressive increase in plasma potassium concentration during anesthesia, which could not be attributed to malignant hyperthermia, hyperkalemic periodic paralysis, metabolic acidosis, or administration of calcium channel blocking agents such as verapamil. Hyperkalemia was the most likely precipitating factor for the severe bradycardia observed during anesthesia in one of the horses following premedication with dantrolene. Progressive hyperkalemia following dantrolene administration has been described in dogs, pigs, and human patients and has generally been attributed to concomitant administration of verapamil. In a review of dantrolene-associated complications in 368 human patients, only 12 (3.3%) patients developed hyperkalemia in the absence of concurrent administration of a calcium channel blocker, and the hyperkalemia in those patients was ultimately attributed to renal failure or suspected malignant hyperthermia. Results of other studies indicate that administration of dantrolene without any other concurrent medications causes an increase in plasma potassium concentration in nonanesthetized human patients and anesthetized dogs and pigs.

To our knowledge, the effect of dantrolene administration specifically on plasma potassium concentration in nonanesthetized and exercise-conditioned horses has not been evaluated, although dantrolene administration to healthy horses and horses with chronic exertional rhabdomyolysis does appear to reduce postexercise serum CK activity with no clinically apparent adverse effects.

In the present study, when horses were premedicated with dantrolene, the CO and cardiac index progressively declined from T1 through T4. Subsequently, we were unable to obtain valid data for calculation of the CO for 5 of the 6 horses at T5 through T7, and we suspect that this was caused by a continued decrease in CO that interfered with the successful generation of valid lithium dilution curves. Cardiac output is influenced by many physiologic and pathological factors, including alterations in heart rate, cardiac contractility, systemic vascular resistance, systemic arterial pressure, and intrathoracic pressure. In the present study, significant decreases in systolic and mean arterial pressures during anesthesia were observed when horses were premedicated with dantrolene but not water, which suggested that dantrolene induced changes in CO that contributed to the progressive decrease in systemic arterial pressure during anesthesia. Furthermore, when horses were premedicated with dantrolene, the mean heart rate declined slightly (2 to 4 beats/min) but significantly during anesthesia, which might also have contributed to the progressive decrease in CO. Although 2 of 6 clinically normal horses developed severe bradyarrhythmias during anesthesia following premedication with dantrolene in the present study, sole administration of dantrolene has not been associated with adverse effects on heart rate or rhythm, blood pressure, or CO in other species. Consequently, the findings of the present study suggested that the cardiovascular effects of dantrolene are more pronounced in horses than in other species. Further studies that use methods other than lithium dilution to measure CO are necessary to determine the effect of dantrolene at doses < 6 mg/kg on the cardiovascular function of conscious and anesthetized horses.

It was difficult to obtain valid lithium dilution curves to assess changes in CO when horses were premedicated with dantrolene in the present study. The first CO measurement was not obtained until at least 75 minutes after premedication when the blood dantrolene concentration was approaching its peak, and the magnitude of the decrease in CO induced by dantrolene might have been better documented in individual horses had CO been measured prior to and shortly after premedication. However, measurement of CO is inherently challenging, and several drugs commonly used in horses such as xylazine, ketamine, and lidocaine adversely affect the function of lithium-dilution CO sensors at clinically relevant concentrations in vitro. Interference of dantrolene with the lithium-dilution CO sensor has not been previously reported. In another
a decrease in CO similar to that observed in the present study was observed in horses with plasma dantrolene concentrations that were substantially lower than those for the horses of the present study, which suggests that the decrease in CO observed following premedication with dantrolene was a true physiologic alteration and not the result of dantrolene interfering with the lithium-dilution sensor used to calculate the CO. Subsequent to the present study, 2 studies were published in which xylazine administration to conscious or anesthetized horses adversely affected the lithium-dilution CO sensor and caused overestimation of the CO. Although the voltage indicator display was favorable for all measurements analyzed in the present study, actual voltage measurements were not evaluated; therefore, we cannot definitively exclude the possibility that xylazine administration during anesthesia induction had an effect on the CO measurements. However, the effects of xylazine on voltage sensors are transient, and all horses in the present study received the same dose of xylazine during induction of both anesthetic sessions, and a reduction, rather than an increase, in CO was observed only when horses were premedicated with dantrolene. Even though results of the present study suggested that dantrolene has a physiologic effect on the cardiovascular variables of anesthetized horses, these findings should be validated with the use of an alternative method for measurement of CO such as thermodilution.

Results of other studies indicate that dantrolene decreases serum CK activity in exercise-conditioned and anesthetized horses. Following premedication with water in the present study, serum CK activity increased after anesthesia in all horses and was increased from the reference interval in 3 of the 6 horses, whereas following premedication with dantrolene, serum CK activity decreased after anesthesia in 2 horses and remained within or almost within the reference interval in 3 horses.

The horse that inhaled the endotracheal tube during recovery from anesthesia following dantrolene premedication and had to be reanesthetized developed clinical signs of triceps myopathy that were accompanied by a progressive and profound increase in serum CK activity during the 24 hours immediately after the incident. Although this might be interpreted as a treatment failure, consideration should be given to the fact that this horse had consistently low plasma dantrolene concentrations during the planned anesthetic session and, unlike the other study horses, was reanesthetized approximately 3.5 hours after dantrolene administration and subsequently spent several hours in lateral recumbency. Additionally, this horse was the heaviest and most temperamental horse enrolled in the study, and the number of attempts required for it to stand after both planned anesthetic sessions was nearly twice that required by the other horses. Thus, it is likely that considerable muscle trauma in this horse overwhelmed any protective effect of dantrolene on serum CK activity, although an increase in CK activity resulting from muscle hypoperfusion subsequent to potential adverse effects of dantrolene on CO and arterial blood pressure cannot be excluded.

Further research in which a reliable model for induction of anesthetic myopathy is used would be beneficial for elucidating the efficacy of dantrolene for preventing anesthesia-induced increases in serum CK activity and determining the optimal plasma dantrolene concentration to maximize beneficial treatment effects and minimize adverse effects. Although IV administration of dantrolene might circumvent bioavailability issues and provide more predictable plasma concentrations, the inconvenience and expense associated with IV dantrolene preparations currently limit their use in horses.

Premedication with dantrolene was tentatively associated with generalized weakness that impaired the recovery of a draft horse from anesthesia. In that report, food was withheld from the horse for 15 hours prior to premedication with dantrolene at a dose of 9 mg/kg, PO, and plasma dantrolene concentrations were not determined. The horse apparently recovered normally immediately after anesthesia but became recumbent 30 minutes after achieving a standing position and had a serum CK activity (10,293 U/L) markedly increased from the reference interval 18 hours after anesthesia. Currently available evidence suggests the plasma dantrolene concentration in that horse was likely negligible because of the extended period during which feed was withheld prior to dantrolene administration. In the present study, premedication of healthy horses with dantrolene was not detrimental to the quality or duration required for anesthesia recovery, despite the substantial plasma dantrolene concentrations most of the horses had throughout anesthesia.

Although results of the present study suggested that premedication with dantrolene (6 mg/kg, nasogastrotrically) 1 hour prior to anesthesia prevented muscle damage in healthy horses without negatively affecting their recovery from anesthesia, this practice cannot be recommended until concerns regarding hyperkalemia and adverse cardiovascular effects associated with dantrolene administration are clarified. Given the findings of the present study, we recommend serial monitoring of plasma potassium concentration in all horses premedicated with dantrolene. Also, dantrolene should not be administered to horses with suspected or known hyperkalemic periodic paralysis.

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Footnotes

b. Dantrolene sodium, 100-mg capsules, IMPAX Laboratories Inc, Hayward, Calif.
c. Large Animal Control Center, Draeger Medical Inc, Telford, Pa.
p. PASS PORT 2 physiologic monitor, Datascience, Malwhav, NJ.
e. DTX Plus, Becton Dickinson Inc, Franklin Lakes, NJ.
h. CAHFS Equine Analytical Chemistry Laboratory, University of California-Davis, Davis, Calif.
i. Neuromuscular Diagnostic Laboratory, College of Veterinary Medicine, University of Minnesota, Saint Paul, Minn.

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