

Effect of oral administration of dantrolene sodium on serum creatine kinase activity after exercise in horses with recurrent exertional rhabdomyolysis

Erica C. McKenzie, BVMS, PhD; Stephanie J. Valberg, DVM, PhD;
Sandra M. Godden, DVM, DVSc; Carrie J. Finno, BSc; Michael J. Murphy, DVM, PhD

Objective—To determine the effect of oral administration of dantrolene sodium on serum creatine kinase (CK) activity after exercise in horses with recurrent exertional rhabdomyolysis (RER).

Animals—2 healthy horses and 5 Thoroughbreds with RER.

Procedure—3 horses received 2 doses of dantrolene (4, 6, or 8 mg/kg, PO, with and without withdrawal of food) 2 days apart; 90 minutes after dosing, plasma dantrolene concentration was measured spectrofluorometrically. On the basis of these results, 5 Thoroughbreds with RER from which food was withheld received dantrolene (4 mg/kg) or an inert treatment (water [20 mL]) orally 90 minutes before treadmill exercise (30 minutes, 5 d/wk) during two 3-week periods. Serum CK activity was determined 4 hours after exercise. Plasma dantrolene concentration was measured before and 90 minutes after dosing on the first and last days of dantrolene treatment and before dosing on the first day of the inert treatment period.

Results—90 minutes after dosing, mean \pm SEM plasma dantrolene concentration was 0.62 ± 0.13 and $0 \mu\text{g/mL}$ in the dantrolene and inert treatment groups, respectively. Serum CK activity was lower in dantrolene-treated horses (264 ± 13 U/L), compared with activity in water-treated horses ($1,088 \pm 264$ U/L). Two horses displayed marked muscle stiffness on the inert treatment.

Conclusions and Clinical Relevance—In 5 horses with RER from which food had been withheld, 4 mg of dantrolene/kg administered orally provided measurable, though variable, plasma concentrations and significantly decreased serum CK activity after exercise in 4 of those horses. (*Am J Vet Res* 2004; 65:74–79)

spastic neuromuscular disorders as well as in the treatment and prevention of **malignant hyperthermia (MH)** and neuroleptic malignant syndrome.^{1,2} Dantrolene modifies excitation-contraction coupling in skeletal muscle via suppression of calcium release from the sarcoplasmic reticulum. This action most likely occurs through interaction of dantrolene with the skeletal muscle calcium-release channel.³ The drug is believed to bind to the calcium-release channel and modify activation of this channel by calmodulin and calcium.³⁻⁵

Dantrolene diminishes muscle damage induced by prolonged exercise in rats⁶ and administration of suxamethonium in humans.⁷ It also attenuates the symptoms of traumatic muscle contracture in human athletes with no apparent detrimental impact on performance, compared with the effect of a placebo compound.⁸ In humans, dantrolene has been reported^{9,10} to control or ameliorate exertional rhabdomyolysis associated with disorders in oxidative phosphorylation and MH. In general, it is not clear whether the beneficial effects of dantrolene are a result of a primary effect upon the calcium-release channel or a secondary effect resulting from alterations in calcium regulation in muscle.

In horses, oral administration of dantrolene has been used to treat MH-like episodes¹¹⁻¹³ and treat and prevent muscle damage associated with anesthesia¹⁴ and exertional rhabdomyolysis.¹⁵⁻¹⁷ However, there is wide variation among the dosages of dantrolene recommended for treatment of these conditions, perhaps because many dosage suggestions have been extrapolated from studies^{11,13,14,18} in other species. Reports^{14,18} of adverse effects of dantrolene in horses include recumbency after anesthesia in association with oral administration of 9 mg of dantrolene/kg and ataxia, weakness, and trembling after IV administration. There are colloquial reports of high hepatic enzyme activity in horses receiving dantrolene orally.¹⁹ In horses, a safe and effective dose of dantrolene is undetermined at present, and controlled clinical trials to confirm the efficacy of dantrolene in the prevention of the conditions for which its use has been recommended have not been performed.¹⁷

Exertional rhabdomyolysis causes pain and muscle necrosis in approximately 5% of racing Thoroughbreds.²⁰ In a subset of Thoroughbreds, exertional rhabdomyolysis is associated with an abnormality in intramuscular calcium regulation similar to that documented in humans and swine with MH; this form is referred to as **recurrent exertional rhabdomyolysis (RER)**.^{21,22}

Dantrolene sodium is a lipid soluble hydantoin analogue.¹ In humans, it is used in the treatment of

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From the Departments of Clinical and Population Sciences (McKenzie, Valberg, Godden, Finno) and Veterinary Diagnostic Medicine (Murphy), College of Veterinary Medicine, University of Minnesota, St Paul, MN 55108. Dr. McKenzie's present address is Department of Physiological Sciences, 264 McElroy Hall, Oklahoma State University, Stillwater, OK 74078.

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Address correspondence to Dr. McKenzie.

Notable reductions in myoplasmic ionized calcium concentrations (measured by calcium selective microelectrodes) in biopsy specimens of intercostal muscle have been detected in horses with exertional rhabdomyolysis and humans with MH after oral and IV administration of dantrolene.^{23,24} To date, no controlled clinical exercise trials have been performed to determine whether dantrolene is beneficial for exertional rhabdomyolysis in horses.¹⁷

The purpose of the study reported here was to determine the effect of oral administration of dantrolene sodium on serum creatine kinase (CK) activity after exercise in horses with RER. The investigation was designed to assess whether oral administration of 4 mg of dantrolene/kg to horses with RER 90 minutes prior to exercise would achieve measurable serum concentrations of the drug, affect serum CK activity measurements after exercise, and diminish clinical signs of exertional rhabdomyolysis without inducing hepatotoxicity. Our hypothesis was that serum CK activity after exercise would be lower in horses with RER that received 4 mg of dantrolene/kg orally 90 minutes prior to exercise than in horses with RER that received an inert treatment. Furthermore, an objective of the study was to evaluate the impact of feeding on the absorption of dantrolene administered via the oral route because other pharmacokinetic studies^{18,25} appear to have been performed only in horses from which food was withheld.

Materials and Methods

Animals—Seven horses (including 5 Thoroughbreds) were used in the study. Five of the 7 horses (the 5 Thoroughbreds) had RER, which was confirmed in a previous study²¹ on the basis of increased sensitivity of excised intact intercostal muscle bundles to caffeine, compared with findings in control horses. Two clinically normal non-Thoroughbred mares (horses A and B) and 1 Thoroughbred stallion with RER (horse C) were used in a preliminary study to determine the optimum dose of dantrolene and conditions of administration for use in a crossover treatment trial in 5 Thoroughbreds with RER. The study was approved by the Animal Care and Use Committee of the University of Minnesota.

Procedure—After food was withheld for 12 hours, horses A, B, and C were administered a single dose of dantrolene sodium^a orally (4, 6, and 8 mg/kg, respectively). To administer the medication, dantrolene-containing capsules were opened, emptied into a syringe, and mixed with 20 mL of water. For analysis of plasma concentrations of dantrolene, blood samples were collected in tubes containing EDTA before and at 90 minutes after administration of the medication (when plasma dantrolene concentration was presumed to peak¹⁸). Analysis of plasma dantrolene concentration was performed at a commercial laboratory^b by use of spectrofluorometry (limit of detection, 0.2 µg/mL). In each horse, a neurologic examination was performed before and 90 minutes after administration of dantrolene. The neurologic examination consisted of a cranial nerve evaluation, several ambulatory neurologic tests (responses to tight turns during walking [serpentine path], tail pulling during walking, and walking with the head elevated), and assessment of the horse's ability to step over three 6-inch-high cavaletti. Two days later, each horse was again assessed in a similar manner after receiving the same dose of dantrolene as before; however, on this occasion, each horse had access to 5 flakes of hay during the night prior to dosing.

Dantrolene was not detected in plasma samples obtained from the 3 horses prior to dosing, regardless of whether food had been withheld or not. When food had been available, dantrolene was not detected in plasma samples obtained 90 minutes after dosing in any of the horses. However, when food had been withheld, plasma concentrations of dantrolene at 90 minutes after administration were 0.7 µg/mL, 0.6 µg/mL, and 1.2 µg/mL in horses A, B, and C, respectively. None of the horses displayed any signs of neural dysfunction or muscular weakness after receiving either of their doses of dantrolene. On the basis of these findings, a dose of 4 mg of dantrolene/kg was selected for the crossover treatment trial, and food was to be withheld from horses for 12 hours prior to administration of the medication.

Four Thoroughbred mares (mean age, 10.3 years; range, 9 to 12 years) and a 5-year-old Thoroughbred stallion with RER were used in the crossover treatment trial. The four mares (horses 1 to 4) had been used in previous studies^{26,27} and were known to have abnormally high serum CK activity after exercise. For purposes of this study, the stallion was designated as horse 5. Prior to the study, all horses were trained to a similar level of fitness by being exercised on a high-speed treadmill 5 d/wk for 4 weeks. During the training period, daily exercise consisted of alternating intervals of walking (1.9 m/s), trotting (4.0 m/s), and cantering (7.0 m/s) that were gradually increased to a total of 30 minutes of exercise per day.

A crossover study design with a 2-day washout period between treatments was used; 3 of the 5 horses were randomly selected to receive dantrolene initially, and the other 2 horses received the inert treatment. During the trial period, horses were exercised 5 d/wk; daily exercise consisted of alternating 2-minute intervals of walking (1.9 m/s), trotting (4.0 m/s), and cantering (7.0 m/s) for a total of 30 minutes. Horses remained confined to a stall throughout the trial and were rested on Saturday and Sunday of every week.

Horses were fed a diet^c of grass hay and received 6.4 kg of sweet feed/d to provide approximately 28.8 Mcal of digestible energy/d. Although the daily caloric intake was in excess of the horses' actual requirements, dietary trials in horses with RER have determined that a high caloric intake of approximately 28.8 Mcal/d (providing 40% of the digestible energy as starch) greatly increases the propensity for episodes of rhabdomyolysis in these animals.^{26,27} Throughout the trial, food was withheld from horses for a 12-hour period (ie, overnight) prior to each day of exercise (ie, 5 nights/wk).

Ninety minutes prior to exercise (Monday through Friday), horses received either the inert treatment (20 mL of water, PO) or dantrolene^a (4 mg/kg mixed in 20 mL of water, PO). Both treatments were administered via syringe, and each treatment was administered for 3 weeks (ie, 15 administrations/horse). Treatments were not administered on Saturday or Sunday of any week. After the final weekend of the 3-week period (ie, after the 2-day washout interval), horses received the other treatment 90 minutes prior to exercise (Monday through Friday) during a second 3-week period. Every weekday, blood samples were collected 4 hours after the discontinuation of exercise via venipuncture of a jugular vein for assessment of serum CK activity. One investigator (ECM) administered treatments, and another investigator (CJF) exercised the horses on the treadmill, observed the horses for signs of muscle stiffness, and collected the blood samples. Serum CK activity was analyzed at another laboratory, and the staff there was unaware of the treatments administered to each horse; for each sample, results were provided the day after its submission to the laboratory.

Blood samples were also collected for assessment of plasma dantrolene concentration. On the first and last day of

Table 1—Mean \pm SEM of the natural logarithm of serum creatine kinase activity ($\ln\text{CK}_A$) in 5 horses with recurrent exertional rhabdomyolysis (RER) undergoing treadmill exercise and treatment with dantrolene sodium (4 mg/kg) or an inert treatment (20 mL of water) for 3 weeks

Treatment	Horse				
	1	2	3	4	5
Inert (n = 15)	6.81 \pm 0.31 ^a	7.21 \pm 0.26 ^a	5.68 \pm 0.14 ^a	5.38 \pm 0.03 ^a	5.68 \pm 0.02 ^a
Dantrolene (15)	5.55 \pm 0.06 ^b	5.67 \pm 0.08 ^b	5.30 \pm 0.06 ^b	5.22 \pm 0.03 ^b	5.78 \pm 0.06 ^a

n = Number of plasma samples analyzed per horse.
^{a,b}Different superscripts indicate significant ($P < 0.05$) differences in $\ln\text{CK}_A$ values of dantrolene and inert treatments within each horse.

the 3-week treatment periods, blood samples were collected from a jugular vein into EDTA tubes before and 90 minutes after dosing (ie, immediately prior to exercise) from each horse. Dantrolene concentration in plasma obtained from these samples was analyzed as described. In horses receiving the inert treatment, blood samples for determination of plasma dantrolene concentration were collected immediately prior to dosing on the first day of the inert treatment period. All plasma samples for spectrofluorometric analysis were protected from light and frozen at -80°C until the time of analysis.

Immediately prior to commencement of the crossover trial and at the end of each 3-week treatment period, blood samples were also obtained from all horses for serum biochemical analyses. Serum concentrations of sodium, chloride, potassium, magnesium, phosphorus, calcium, creatinine, albumin, and bilirubin and activities of sorbitol dehydrogenase (SDH) and γ -glutamyltransferase were determined for each sample. Samples were kept on ice and analyzed within 12 hours of collection.

Statistical analyses—Serum CK activity after exercise was the dependent variable of interest. However, these data did not conform to normal distribution, so they were transformed to the natural logarithm of serum CK activity ($\ln\text{CK}_A$) prior to statistical analysis. Serum CK results were analyzed in a mixed model approach by use of a 1-way ANOVA, controlling for repeated measures.^d Values of $P < 0.05$ were considered significant. The effect of treatment on $\ln\text{CK}_A$ in individual horses was also examined by use of an ANOVA after stratifying by horse. Serum biochemical data values were compared with laboratory reference ranges. Values are expressed as mean \pm SEM.

Results

Adverse effects of treatments—Neurologic deficits, muscular weakness, or exercise intolerance was not observed in any of the horses throughout the crossover trial. During the 3-week period in which the inert treatment was administered, 2 horses (horses 1 and 2) had an episode of sweating, stiffness, and signs of muscle pain immediately after exercise. The episodes occurred on the first and the ninth day after commencing the inert treatment in horses 1 and 2, respectively. At the time of these episodes, the serum CK activity of horses 1 and 2 was 16,910 and 5,205 U/L, respectively (reference range, 79 to 556 U/L).

Serum CK activity after exercise—After exercise, serum CK activity and $\ln\text{CK}_A$ were significantly greater in horses that received the inert treatment (serum CK activity, $1,088 \pm 264$ U/L; $\ln\text{CK}_A$, 6.17 ± 0.01) than in horses that received dantrolene (serum CK activity, 264 ± 13 U/L; $\ln\text{CK}_A$, 5.51 ± 0.004). In 4 of 5 horses, administration of dantrolene significantly reduced val-

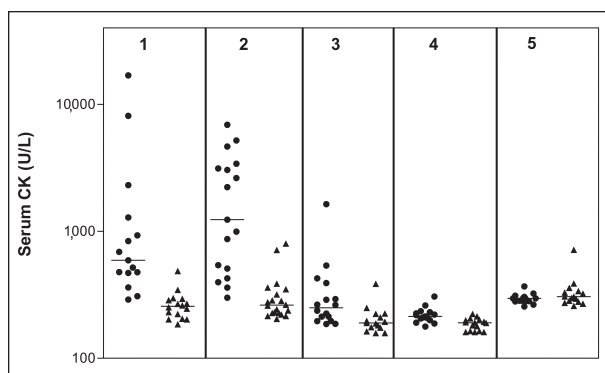


Figure 1—Scatterplot of serum creatine kinase (CK) activity 4 hours after exercise in 5 horses (designated 1 to 5) with recurrent exertional rhabdomyolysis (RER) receiving either dantrolene (4 mg/kg, PO; triangles) or an inert treatment (20 mL of water, PO; circles). Horizontal bars indicate median serum CK activity for each horse.

Table 2—Plasma dantrolene concentrations ($\mu\text{g/mL}$) detected 90 minutes after administration of dantrolene (4 mg/kg, PO) on the first and last days of a 3-week treatment period and before treatment with an inert agent (20 mL of water, PO) on the first day of a 3-week treatment period in 5 horses with RER undergoing treadmill exercise

Horse	Treatment		
	Dantrolene		Inert
	First day (90 minutes after treatment)*	Last day (90 minutes after treatment)*	First day (before treatment)
1	0.0 (487)	0.8 (345)	0.0 (16,910)
2	0.6 (283)	0.0 (800)	0.0 (2,230)
3	1.2 (224)	0.7 (158)	0.0 (293)
4	0.5 (199)	0.9 (161)	0.0 (210)
5	0.4 (295)	1.1 (258)	0.0 (311)

*Dantrolene was not detected in the plasma of horses prior to dosing on the first and last days of the 3-week period of treatment with dantrolene. Numbers in parentheses represent the serum CK activity detected 4 hours after exercise.

ues of $\ln\text{CK}_A$ after exercise, compared with the effect of the inert treatment (Table 1; Fig 1). However, there was considerable interindividual variation in serum CK activity. Horse 4 did not have high serum CK activity at any of the sampling time points throughout the trial regardless of treatment. Horse 5 had mildly high serum CK activity (715 U/L) after exercise on 1 occasion during treatment with dantrolene.

Plasma dantrolene concentrations—Dantrolene was not detected in plasma samples obtained from horses prior to dosing on the first and last day of the 3-week period of treatment with dantrolene or those

Table 3—Mean \pm SEM (range) serum hepatic enzyme activities and total bilirubin, albumin, creatinine, and calcium concentrations in 5 horses with RER treated prior to treadmill exercise for 3 weeks with dantrolene sodium (4 mg/kg, PO) or an inert agent (20 mL of water, PO)

Variable	Reference range	Baseline (before treatment) value	End of dantrolene treatment (week 3 value)	End of inert treatment (week 3 value)
Sorbitol dehydrogenase activity (U/L)	1.0–8.0	3.6 \pm 1.04 (2.0–7.5)	3.2 \pm 1.02 (2.0–7.2)	2.7 \pm 0.52 (2.0–4.2)
γ -Glutamyltransferase activity (U/L)	4–48	12.0 \pm 1.22 (8–15)	13.2 \pm 1.02 (11–16)	13.0 \pm 0.82 (11–15)
Total bilirubin concentration (mg/dL)	0.4–2.3	1.6 \pm 0.20 (1.0–2.2)	1.7 \pm 0.17 (1.1–2.1)	1.6 \pm 0.24 (1.3–2.2)
Albumin concentration (g/dL)	2.9–4.2	3.5 \pm 0.10 (3.1–3.7)	3.4 \pm 0.06 (3.2–3.5)	3.3 \pm 0.13 (3.0–3.6)
Creatinine concentration (mg/dL)	0.9–1.8	1.2 \pm 0.07 (1.0–1.4)	1.4 \pm 0.14 (1.0–1.8)	1.2 \pm 0.22 (0.9–1.8)
Calcium concentration (mg/dL)	10.2–13.0	11.4 \pm 0.21 (10.7–12.0)	11.7 \pm 0.26 (11.3–12.7)	11.4 \pm 0.27 (10.7–11.9)

obtained prior to dosing on the first day of the period of treatment with water. Ninety minutes after administration of dantrolene on the first day of the dantrolene treatment period, mean plasma dantrolene concentration in the 5 horses was $0.54 \pm 0.19 \mu\text{g/mL}$ (Table 2). On the last day of dantrolene treatment 90 minutes after dosing, mean plasma dantrolene concentration was $0.70 \pm 0.19 \mu\text{g/mL}$.

Serum biochemical data—Serum hepatic enzyme activities and total bilirubin concentration did not exceed the upper limit of the reference ranges in any of the horses before or after 3 weeks of treatment with either dantrolene or water (Table 3). Plasma albumin and creatinine concentrations were also within reference limits in all horses. Serum concentrations of sodium, potassium, chloride, phosphorus, magnesium, and calcium were within reference limits in all horses (irrespective of treatment).

Discussion

In the study reported here, oral administration of 4 mg of dantrolene/kg to horses with RER 90 minutes prior to exercise almost completely ameliorated increases in serum CK activity and clinical signs of exertional rhabdomyolysis after exercise. The most dramatic improvement in serum CK activity was observed in horses 1 and 2 that developed clinical signs of exertional rhabdomyolysis while receiving the inert treatment but not when receiving dantrolene. Anecdotaly, dantrolene has been reported to have little effect in preventing exertional rhabdomyolysis in horses.¹⁵ However, previous recommendations for the use of dantrolene for treatment and prevention of exertional rhabdomyolysis in horses have included low doses (frequently $\leq 2 \text{ mg/kg}$) and administration in feed; timing of drug administration with regard to exercise was seldom considered.^{15,16,19} In the study reported here, plasma concentrations of dantrolene were undetectable in fed horses receiving doses of 8 mg of dantrolene/kg orally; thus, it is not surprising that use of dantrolene to prevent exertional rhabdomyolysis in horses has been apparently ineffectual because most treated horses would have had access to feed.¹⁵ In our study, it was not determined whether delayed or reduced absorption

played a role in the inability to detect plasma dantrolene concentrations $> 0.2 \mu\text{g/mL}$ in fed horses. However, feeding may impact both maximal absorption and the time to achieve peak plasma concentration of dantrolene. In horses, the minimum period of food withdrawal required to achieve therapeutic plasma concentrations of dantrolene and the time that therapeutic concentrations may be maintained with a single dose of dantrolene remain to be elucidated.

Results of pharmacokinetic studies^{18,25} in horses from which food has been withheld have indicated that oral administration of dantrolene results in peak blood concentration in approximately 90 minutes. In 1 study,¹⁸ a dose of 4 mg of dantrolene/kg administered orally (via stomach tube) resulted in peak blood dantrolene concentrations of approximately $1.42 \mu\text{g/mL}$ at 90 minutes.¹⁸ In another study,²⁵ a single 1-g dose (1.87 to 2.35 mg/kg) of dantrolene administered orally to 8 Standardbred mares resulted in peak plasma dantrolene concentrations of 140 to 345 ng/mL (0.14 to $0.35 \mu\text{g/mL}$) after 60 to 180 minutes.²⁵ In our study, we chose to exercise the horses 90 minutes after administration of the treatments because plasma dantrolene concentration of $0.7 \mu\text{g/mL}$ had been achieved with oral administration of 4 mg of dantrolene/kg in our preliminary trial. The horses with RER had considerably lower peak plasma dantrolene concentrations during the crossover trial (mean \pm SEM, $0.62 \pm 0.13 \mu\text{g/mL}$), compared with results of a study by Court et al¹⁸ that involved administration (via nasogastric tube) of a similar dose of dantrolene (4 mg/kg) in 500 mL of physiologic saline (0.9% NaCl) solution to horses from which food was withheld; in the latter study, mean \pm SD peak plasma dantrolene concentration was $1.42 \pm 0.28 \mu\text{g/mL}$.¹⁸ The disparate results of these 2 studies are likely a consequence of differences in the method of administration. In the current study, medication was carefully administered to each horse via syringe, which was likely to be less effective in the delivery of drugs to the intestinal tract than that achieved via nasogastric intubation. The study by Court et al¹⁸ also used a different method to measure whole blood dantrolene concentration from that used in our study. Those investigators used a combination of solvent extraction, column chromatography, and fluo-

rometry that provided a lower minimum detection limit (0.1 µg/mL) than the spectrofluorometric assay used in our study.

In the study reported here, plasma concentrations of dantrolene differed between the 2 samples obtained for each horse and also among horses. For example, on 1 occasion horses 1 and 2 had plasma dantrolene concentrations below the minimum detection limit (despite the withholding of food prior to drug administration), and the second measurement of plasma dantrolene concentration was ≥ 0.6 µg/mL. In humans receiving dantrolene orally, similar inter- and intraindividual variations in plasma dantrolene concentration have been identified, and these have resulted in poor correlations between the administered dose and serum or blood concentrations of dantrolene.^{28,29} Several factors may explain the apparent failure to achieve consistent plasma dantrolene concentrations after oral administration, including the impact of the acidity and emptying rate of stomach contents on intestinal absorption.²⁸ In addition, there may be individual variability in dantrolene clearance.²⁸ The processing and handling of plasma samples can also influence plasma dantrolene concentration. Dantrolene breaks down readily on exposure to light²; consequently, plasma samples were protected from light and frozen soon after sampling in the study of this report. Although IV administration of dantrolene provides more predictable plasma concentrations, the cost of the drug and its insoluble nature, limited availability, and potential for adverse effects complicate its administration by this route in horses.^{2,16,18,19,30} In our study, a beneficial effect of dantrolene in horses with RER was detected after oral administration, despite limitations in absorption and clearance; administration of 4 mg of dantrolene/kg via syringe 90 minutes prior to exercise to horses from which food was withheld appeared to be an effective means to control RER in horses in training. Although no neurologic deficits or weakness was noted after administration of 4 mg of dantrolene/kg to the horses in our study, it is possible that dantrolene could negatively affect athletic performance, particularly at higher doses. At present, dantrolene is restricted from use in racing horses in the United States.

During muscle excitation-contraction coupling, calcium is released from the sarcoplasmic reticulum via the calcium-release channel into the myoplasm where it initiates contraction of myofilaments. Muscle relaxation is an energy-dependent process that requires calcium to be pumped back into the sarcoplasmic reticulum by calcium ATPase. In horses with RER, dantrolene may be beneficial because it slows the release of calcium from the sarcoplasmic reticulum via the calcium-release channel.³ By use of calcium-selective microelectrodes, Lopez et al²³ reported that myoplasmic calcium concentrations are high, and administration of dantrolene lowers myoplasmic calcium concentrations in unspecified breeds of horses with active rhabdomyolysis.²³ Dantrolene is also frequently used to treat rhabdomyolysis in humans with MH. Many of these individuals have a mutation in the gene that encodes the skeletal muscle, calcium-release channel (the RYR1 gene).³¹ There are some physiologic similarities

between RER and MH, such as low contracture thresholds of skeletal muscle in response to halothane, caffeine, and potassium.²¹ However, some findings differ from those observed in similar investigations of humans with MH. In horses with RER, 4-chloromethyl-cresol does not induce a lower threshold for muscle contracture response as it does in humans with MH; furthermore, ryanodine binding to the calcium-release channel in isolated sarcoplasmic reticulum membranes is similar in both RER-affected and control horses.³² A defect in the mechanism of intracellular calcium regulation is substantiated by results of a study²² that indicated that caffeine produces a greater flux of calcium into the myoplasm of cultured muscle cells from horses with RER, compared with that detected in cells from control horses. These findings, combined with the apparent suppressive effects of dantrolene on rhabdomyolysis in horses with RER, support the hypothesis that RER is a novel defect in intramuscular calcium regulation.

Dantrolene also has several other physiologic effects, some of which are independent of its impact on calcium regulation; these include marked central GABAergic effects and sedation,² inhibition of adrenocortical aldosterone and cortisol production,³³ inhibition of glucose-stimulated insulin release from isolated pancreatic islets,³⁴ and reduced caffeine-induced catecholamine release from the adrenal medulla.³⁵ Whether such effects of dantrolene play a role in the amelioration of rhabdomyolysis in horses with RER is unknown.

In horses and humans, dantrolene undergoes hepatic microsomal metabolism to produce an active metabolite 5-hydroxydantrolene.^{25,36} Dantrolene and its metabolites are primarily excreted in the urine, but small amounts are excreted in bile.^{18,36} Dantrolene is not detectable in urine 24 hours after oral administration of a single 1-g dose in horses; however, 5-hydroxydantrolene is detectable in urine for at least 30 hours after dosing.²⁵ In horses, dantrolene undergoes rapid clearance with an elimination half-life (\pm SEM) of 129 ± 8 minutes.¹⁸ There are concerns that dantrolene may have hepatotoxic effects in horses because of such adverse effects in humans.³⁷ The adverse hepatic effects may result from interaction of dantrolene with the hepatic mixed-function oxidase system and reduction in cytochrome P₄₅₀ content.^{38,39} In humans, hepatotoxic effects of dantrolene develop after long-term administration (> 2 months' duration), appear to be dose-dependent, and are frequently reversible upon withdrawal of the drug.³⁷ In the horses of the study reported here, hepatotoxicosis did not appear to develop because serum liver enzyme activities and bilirubin concentrations were within reference limits on the final day of the 3-week period of treatment with dantrolene. Furthermore, in plasma samples obtained prior to dosing on the last day of the 3-week period of daily treatment with dantrolene, the drug was undetectable, which indicated no measurable plasma accumulation. However, because there is limited information on long-term administration of dantrolene in horses, it is recommended that serum hepatic enzyme activities (specifically SDH) be monitored at monthly

intervals (or more frequently) if the drug is administered for extended periods.¹⁵

Results of the study reported here suggest that dantrolene (administered orally 90 minutes prior to exercise at a dose of 4 mg/kg to horses from which food has been withheld) may be a useful adjunctive treatment in the management of horses with RER. Over a 3-week period in which dantrolene was administered daily, no evidence of hepatotoxicosis or other adverse effects were noted in the study horses. However, to assess further the usefulness of dantrolene in the treatment and prevention of RER in horses, additional clinical investigations and studies on the effects of dantrolene in vitro on intramuscular calcium fluxes and myofiber contracture thresholds in horses with RER are needed.

^aDantrium (dantrolene sodium), 100-mg capsules, Proctor & Gamble Pharmaceuticals, Cincinnati, Ohio.

^bNational Medical Services, Willow Grove, Pa.

^cHorse feed supplied by Hallway Feeds, Lexington, Ky.

^dProc Mixed in SAS, version 8.0, SAS Institute Inc, Cary, NC.

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