

# Clinical Evidence Article

## The efficacy of dantrolene sodium in controlling exertional rhabdomyolysis in the Thoroughbred racehorse

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### Summary

**Reasons for performing study:** Dantrolene sodium (Dantrium) has been used extensively for the treatment of myopathies in man and anecdotal evidence suggests it is of clinical benefit in the control of exercise-induced rhabdomyolysis (ER) in racehorses, although data to support this are currently lacking.

**Objectives:** To investigate the efficacy of oral dantrolene sodium in controlling ER in a randomised, double-blind, placebo-controlled crossover trial involving 77 Thoroughbred racehorses in Newmarket, UK.

**Methods:** Horses were treated on 2 occasions 1 week apart, with treatment days coinciding with a return to exercise following 2 days box rest on each occasion. For the first treatment, each horse was randomly selected to receive either 800 mg dantrolene sodium or a colour-matched placebo administered orally 1 h before exercise. This was followed by crossover to the other treatment on the second occasion, with each horse thereby acting as its own control.

Degree of ER was assessed using rising serum creatine kinase (CK) levels, by subtracting pre-exercise blood CK levels from those measured in 6 h post exercise blood samples. For each horse, the difference in change between pre- and post exercise CK values between placebo and dantrolene treatments was calculated, with positive values indicating a greater rise with placebo than with dantrolene sodium treatment.

**Results:** The overall mean difference for all horses was +104.8 iu/l and the null hypothesis, that there was no true difference in non-normally distributed post exercise rises in CK values between placebo and dantrolene treatments, was rejected ( $P = 0.0013$ ) using the nonparametric Wilcoxon signed rank test. Additionally, no horses given dantrolene sodium showed clinical signs of ER, whereas 3 horses given the placebo developed ER following exercise. The incidence of ER in the study was 4% (3/77).

**Conclusions:** The results confirmed that oral administration of dantrolene sodium, 1 h before exercise, had a statistically significant effect on reducing the difference between pre-

and post exercise plasma CK levels compared with a placebo in the same animals, and preventing clinical ER in susceptible individuals.

**Potential relevance:** This study suggested that dantrolene sodium is of use in controlling ER in the Thoroughbred racehorse. Further investigation into pre- and post exercise myoplasmic calcium levels and the repeat of the study late in the season when horses receive a much higher energy ration and more strenuous exercise would appear to be warranted.

### Introduction

Exertional rhabdomyolysis (ER) is an intermittently occurring condition that primarily affects the muscles of horses during or following exercise (Harris 1997). Clinical signs range from slight stiffness to immobility (Harris 1991) and may include apparent anxiety, sweating, reluctance to move, gait abnormalities, myoglobinuria and hard, painful, swollen muscles particularly of the hindlimbs (Hodgson 1993; Valberg *et al.* 1993; Harris 1997; McGowan *et al.* 2002).

The condition has been recognised for over a century (Hodgson 1993) and has also been referred to as 'tying-up', 'azoturia', 'set fast' and 'Monday morning disease' (Harris 1991; Valberg *et al.* 1993). Various risk factors have been identified in Thoroughbred racehorses in the UK including female gender, nervous or excitable temperament and younger age; the condition is most common at age 2 years (McGowan *et al.* 2002).

Historically, the condition is more prevalent following a period of rest while being maintained on a high carbohydrate diet (Harris 1997). Diagnosis is based on history, clinical signs and plasma/serum increases in the enzymes creatine kinase (CK) and aspartate aminotransferase (AST) (Valberg *et al.* 1993; Harris 1997; McGowan *et al.* 2002).

The prevalence of ER in racehorses in the UK is approximately 7%, with 80% of trainers having at least one affected horse (McGowan *et al.* 2002). Exertional rhabdomyolysis recurs in 74% of affected individuals with an average of 6 days training lost per episode, suggesting that ER has a major economic

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and welfare impact on the racing industry (McGowan *et al.* 2002); and it is a syndrome with multiple proposed aetiologies, including vitamin and mineral imbalances, endocrinopathies, electrolyte imbalances and metabolic derangements (Hodgson 1993; Valberg *et al.* 1999) which cause inappropriate hypercontraction of muscle fibres, leading to muscle cell damage and eventual cell necrosis (Jones 1989). Regulation of muscle contraction appears abnormal in Thoroughbred horses with recurrent ER, possibly attributable to abnormal intracellular calcium regulation (Lentz *et al.* 1999).

Dantrolene sodium is a skeletal muscle relaxant which acts primarily by affecting calcium flux across the sarcoplasmic reticulum (Ward *et al.* 1986). It has been used in man to suppress the uncontrolled calcium release that underlies the skeletal muscle pharmacogenetic disorder malignant hyperthermia (Fruen 1997), and successfully to prevent recurrent ER (Haverkort-Poels 1987). Dantrolene is used both prophylactically and therapeutically in man, although long-term therapy has been associated with hepatic toxicity (Ward *et al.* 1986). Intracellular calcium levels have been found to be elevated in cases of human ER and treatment with dantrolene has accelerated patients' recovery (Lopez *et al.* 1995a). Elevated myoplasmic calcium levels also occur in horses with ER, and dantrolene has been successful in reducing calcium concentrations and accelerating recovery (Lopez *et al.* 1995b).

Dantrolene sodium has been recommended for the prevention and treatment of ER in horses (Court *et al.* 1987; Jones 1989; Hodgson 1993; Hodgson and Rose 1994; Harris 1997), although data to support its efficacy are currently lacking (Hodgson and Rose 1994; Harris 1997). Anecdotal evidence suggests that the oral form of the drug is of clinical benefit in the control of ER in racehorses.

The aim of this study was to investigate the efficacy of prophylactic use of oral dantrolene sodium (Dantrium capsules)<sup>1</sup> in controlling ER in Thoroughbred racehorses by comparing rises in post exercise CK levels in the same horses after administration of dantrolene sodium or placebo.

## Materials and methods

### Study horses

Horses included in the study were 77 Thoroughbred flat racehorses in 3 training yards in Newmarket, UK. Horses included 21 two-year-olds (27%), 47 three-year-olds (61%), 7 four-year-olds (9%) and 2 five-year-olds (3%) and consisted of 37 colts (48%), 6 geldings (8%) and 34 fillies (44%).

In order to qualify for inclusion in the study, horses must not have exercised for the previous 2 days; 1 horse was withdrawn from the study as it received 30 mins walking exercise prior to collection of the first blood sample and subsequently exhibited a high resting serum CK level (1256 iu). The study was conducted in mid-winter, with an average temperature of 5.4°C on exercise days.

### Study protocol

Horses were investigated on 2 occasions, 1 week apart, coinciding with a return to exercise following 2 days enforced box rest on each occasion. All horses received a minimum of 1 h trotting exercise on each occasion. No horses received any medication between the first and second investigations.

On the first occasion, each horse was randomly selected to receive either dantrolene sodium or a colour-matched placebo administered orally 1 h before exercise. On the second occasion,

horses which had previously received dantrolene sodium crossed-over to the placebo treatment and *vice versa*, with each horse thereby acting as its own control.

The dantrolene sodium and placebo treatments were prepared in advance and preloaded in 10 ml syringes labelled A or B. The identities of A and B were known only to the person preparing the treatments, who was not involved in administering it or taking and analysing blood samples. The clinical investigators, trainers, handlers, jockeys and laboratory personnel were masked completely as to the identity and order of treatments. Horses were assigned identification numbers and the treatment administered (A or B) was recorded for each horse on each occasion.

A fixed dose of 800 mg dantrolene sodium powder (the contents of eight 100 mg capsules) was used per horse, based on the amount used by clinicians in Newmarket. The powder was mixed with 9 ml tap water to produce a 10 ml suspension 30 mins prior to administration. The colour-matched placebo was carrot juice<sup>2</sup> given *per os*. Blood samples were taken at the time of treatment (i.e. 1 h pre-exercise) and 6 h post exercise.

### Laboratory methods and definition of ER

All blood samples were collected in lithium heparin blood tubes (S-Monovette Lithium Heparin)<sup>3</sup> and labelled with the horse's number, treatment given (A or B) and whether they were pre- or post exercise samples (AM or PM). Plasma CK levels were measured using the modified (Oliver) N-acetyl cystine method (Rosalki 1967) and degree of ER was assessed by subtracting pre-exercise blood CK levels from those measured in samples taken 6 h post exercise. Using this method, a rise in CK had a positive value and a decrease a negative value. For each horse, the difference in changes in CK values between the placebo ( $P_{diff}$ ) and dantrolene sodium ( $T_{diff}$ ) treatments was calculated by subtracting  $T_{diff}$  from  $P_{diff}$  ( $P_{diff} - T_{diff}$ ). Positive values of  $P_{diff} - T_{diff}$  corresponded to greater rises in CK with the placebo than with dantrolene sodium.

Horses with clinical ER show marked increases in CK (>1000 iu), whereas unaffected horses show little change from resting levels (Harris 1997). This allowed a simple definition of ER.

### Statistical methods

Data were analysed to test the null hypothesis that the true difference in post exercise rises in CK values between placebo and dantrolene sodium treatments ( $P_{diff} - T_{diff}$ ) was zero using the nonparametric Wilcoxon signed rank test. In addition, data were analysed using the standard 2-sample *t* test to test the null hypothesis of no difference in  $P_{diff} - T_{diff}$  between those horses randomly selected to receive placebo first compared to animals receiving dantrolene sodium first. This assessed whether the crossover design with washout between treatments was appropriate. All data were managed using a Microsoft Excel spreadsheet<sup>4</sup> prior to importing into Stata software (Stata 5.0)<sup>5</sup> for statistical analyses, with  $P < 0.05$  used to determine statistical significance.

The number of horses required (*n*) for this crossover study design, using a significance level of 5% and study power of 80%, was calculated using the standard formula:

$$n = 7.84 * (P_0 * [1 - P_1] + P_1 * [1 - P_0]) / (P_1 - P_0)^2$$

where  $P_0$  is the proportion of animals with ER following treatment and  $P_1$  the proportion of affected horses after receiving

**TABLE 1: Creatine kinase (CK) values for each of 3 groups receiving Dantrium or placebo; mean, median, interquartile range and range (iu/l)**

Value	Treatment	Mean	Median	Interquartile range	Range
Pre-exercise CK	Dantrium	207.9	201	173–230	121–402
	Placebo	200.0	192	170–219	130–510
Post exercise CK	Dantrium	223.1	209	181–240	130–856
	Placebo	320.0	221	190–248	150–2883
Pre-/post difference	Dantrium	15.2	8	-6–23	-173–633
	Placebo	120.0	19	3–55	-290–2729
$P_{diff} - T_{diff}$		104.8	12	-8–58	-588–2740

placebo. With  $P_0$  assumed to be 0% (i.e. treatment was expected to be 100% effective) and  $P_1$  estimated at 10% based on previous experience in racehorses in Newmarket (R.C. Pilsworth, unpublished data), the required number of horses for the study was, therefore, 78.

## Results

Values (Table 1) for  $P_{diff} - T_{diff}$  were markedly non-normally distributed (positively skewed; Fig 1) with a median value of +12 iu/l and mean value +104.8 iu/l. The null hypothesis that there was no true difference in post exercise rises in CK values between placebo and dantrolene treatments was rejected ( $P = 0.0013$ ) using the nonparametric Wilcoxon signed rank test. Additionally, CK rises considered diagnostic for ER (>1000 iu/l) (Harris and Mayhew 1998) were seen in 3 horses (incidence of 4%) following administration of the placebo but in none following dantrolene sodium treatment, which is consistent with the treatment being effective in preventing clinical ER in susceptible individuals. Values are shown in Table 2. Of these 3 affected horses, the placebo was the first treatment in 2, while the other received dantrolene sodium first.

Examination of  $P_{diff} - T_{diff}$  values using the standard 2 sample  $t$  test showed there was no statistically significant difference ( $P = 0.94$ ) between horses randomly selected to receive placebo first (mean  $\pm$  s.e. +108.7  $\pm$  76.9 iu/l,  $n = 39$ ) compared to animals receiving dantrolene sodium first (mean  $\pm$  s.e. +100.9  $\pm$  71.2 iu/l,  $n = 38$ ). This indicated that there was likely to have been adequate washout between treatments in the crossover design of this study.

Complete raw data on horse identification, yard, gender, age, CK values,  $P_{diff}$ ,  $T_{diff}$ ,  $P_{diff} - T_{diff}$  and first randomised treatment for the 77 individual horses in the trial ordered by descending  $P_{diff} - T_{diff}$  values are available on request from the EVJ Editorial Office.

## Discussion

The purpose of this study was to investigate the efficacy of oral dantrolene sodium in the control of ER diagnosed by increasing CK levels between pre- and post exercise blood samples in a randomised, double-blind, placebo-controlled crossover trial involving 77 Thoroughbred racehorses in Newmarket, UK. The population of horses investigated reflected a typical cross-section

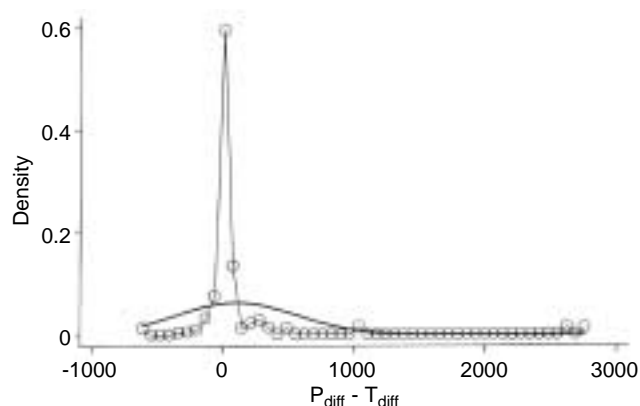


Fig 1: Kernel density plot (○) of  $P_{diff} - T_{diff}$  with superimposed normal distribution demonstrating a markedly non-normal, right skewed distribution.

of Thoroughbred racehorses in flat race training in Newmarket. This population contained 12 (16%) 2-year-old fillies, considered to be most frequently affected by ER (MacLeay *et al.* 1999; McGowan *et al.* 2002). Prior to exercise the horses received 2 days box-rest, which has been shown to increase the frequency of ER in susceptible animals (MacLeay *et al.* 1999), although the stabled horses were fed approximately half their normal training ration, which may have helped prevent some clinical cases of ER (Harris 1997). As the study was conducted in mid-winter, all fillies were assumed to be anoestrus, although no association has been demonstrated between stage of oestrus cycle and ER (Frauenfelder *et al.* 1986).

Degree of ER was assessed by measuring changes in plasma CK levels (Valberg *et al.* 1993; Harris 1997). Affected horses typically show serum CK levels of >1000 iu, whereas unaffected horses show very little increase in serum CK following exercise (Harris 1997). This allows degree of ER to be measured easily. CK is present in the brain and myocardium as well as in skeletal muscle, with several isoenzymes occurring (Harris and Mayhew 1998). The laboratory test used did not distinguish between isoenzymes and it was assumed in this study that all CK changes were muscular in origin. The post exercise samples were taken 6 h after training exercise because plasma CK levels rise after a delay of 5 h from the start of exercise (Volfinger *et al.* 1994) and peak at 6 h (Hodgson and Rose 1994). Practically, this also allowed blood samples to be taken by the yard veterinary surgeon at 'evening stables'. However, plasma CK has a very short half-life (mean 123  $\pm$  28 mins) (Court *et al.* 1987) and a degree of error may have occurred at this point as there was a 20 min interval between the first and last post exercise blood samples being taken, and possible small differences in time of sampling between the different yards.

Dantrolene has been used to control ER in man (Fruen *et al.* 1997) and to prevent malignant hyperthermia (MH) in both pigs and man (Ward *et al.* 1986). It has been recommended for the prevention and treatment of ER in horses, but no data exist regarding its efficacy. Various dose rates have been proposed for

**TABLE 2: Yard and horse identification and creatine kinase (CK) values (iu/l) in 3 horses diagnosed with exertional rhabdomyolysis**

Yard and horse identification	Pre-exercise CK (placebo)	Post exercise CK (placebo)	Pre-exercise CK (dantrolene)	Post exercise CK (dantrolene)
1:27 2-year-old colt	154	2883	263	252
2:15 4-year-old filly	168	27971	188	181
2:18 3-year-old filly	149	1217	144	169

oral dantrolene sodium (Court *et al.* 1987). A dose rate of 2 mg/kg bwt has been proposed (Hodgson and Rose 1994), which is similar to the standard dose of 800 mg used in this study (assuming most horses were between 400–450 kg) and considerably lower than the 10 mg/kg bwt dose rate recommended by Court *et al.* (1987) based on medical data suggesting therapeutic blood concentrations of 2.8–4.2 µg/ml. Dantrolene is metabolised to 5-hydroxydantrolene, which has a similar action to the parent compound and is excreted in the urine (Ward *et al.* 1986). The study by Court *et al.* (1987) did not mention this compound and apparently did not measure levels in blood or urine. This may explain why a lower dose rate appears to be efficacious in practice.

Dantrolene sodium is rapidly and reliably absorbed following oral administration, reaching peak levels within 90 mins and remaining at therapeutic levels for 2 h (Court *et al.* 1987), although these data are again based on measurement of dantrolene sodium alone and it may have a longer effective half-life due to the action of its metabolite. Dantrolene sodium suspension given orally has only a 40% bioavailability (Court *et al.* 1987) but the dose of 2 mg/kg bwt, 1 h prior to exercise, was effective in reducing plasma CK rise in post exercise samples in this study.

The results of this study suggest that a derangement of intracellular calcium regulation may be present in cases of ER. Horses and human individuals with ER demonstrate elevated myoplasmic calcium levels (Lopez *et al.* 1995a,b) and horses with ER show abnormal regulation of muscle contraction (Lentz *et al.* 1999), primarily due to an alteration in muscle cell calcium regulation (Lentz *et al.* 2002). The pathogenesis of ER is still not fully understood; however, the sarcoplasmic reticulum defect responsible for MH does not appear to be the cause of ER (Ward *et al.* 2000). A future study investigating pre- and post exercise myoplasmic calcium levels may help demonstrate that oral dantrolene sodium given 1 h before training has an effect on calcium regulation within the muscle cell.

The overall mean difference in plasma CK change between the placebo and dantrolene sodium treatments was +104.8 iu/l, although the majority of differences were much less than this (median +12 iu/l). This indicated a greater increase in plasma CK levels with the placebo than with the dantrolene sodium treatment. The increase is low, suggesting that most horses did not suffer from clinical ER (CK >1000 iu/l) (Harris and Mayhew 1998) in this study. Additionally, the incidence of ER in the study was 4% (3/77), lower than 7% quoted by McGowan *et al.* (2002). The reasons for this are probably attributable firstly to the management and training practices used in Newmarket to minimise ER, and secondly to the yards being self-selecting in submitting horses for the study.

It would be useful to repeat the study later in the season when horses receive a much higher energy ration and more strenuous exercise, both risk factors associated with ER (MacLeay *et al.* 1999; McGowan *et al.* 2002). However, the null hypothesis that there was no true difference in non-normally distributed post exercise rises in CK values between placebo and dantrolene sodium treatments was rejected ( $P = 0.0013$ ). Additionally, no horses given dantrolene sodium showed clinical signs of ER, whereas 3 horses given the placebo developed signs of ER following exercise. Dantrolene sodium therefore appears to have a role both as a treatment for existing cases of ER (Lopez *et al.* 1995a,b), decreasing recovery times of affected horses and also in the prevention of ER in susceptible animals. Dantrolene sodium is currently used clinically to break the vicious circle of ER, giving

quicker recovery times in affected horses and allowing them to begin exercise again following rest without suffering recurrence.

The results of this study confirmed that dantrolene sodium had a statistically significant effect, reducing rises in post exercise CK levels compared to placebo in the same animals and preventing clinical ER in susceptible individuals, consistent with it being an effective prophylactic treatment for ER.

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### Manufacturers' addresses

<sup>1</sup>Procter and Gamble Pharmaceuticals Ltd. Staines, Surrey, UK.

<sup>2</sup>Eden-Warren, Granovita UK, Wellingborough, Hampshire, UK.

<sup>3</sup>Sarstedt, Nümbrecht, Germany.

<sup>4</sup>Microsoft Corporation, Redmond, Washington, USA.

<sup>5</sup>Stata Corp., College Station, Texas, USA.

### References

- Court, M.H., Engelking, L.R., Dodman, N.H., Anwer, M.S., Seeler, D.C. and Clark, M. (1987) Pharmacokinetics of dantrolene sodium in horses. *J. vet. Pharmacol. Therap.* **10**, 218-226.
- Frauenfelder, H.C., Rosedale, P.D., Ricketts, S.W. and Allen, W.R. (1986) Changes in serum muscle enzyme levels associated with training schedules and stage of the oestrus cycle in Thoroughbred racehorses. *Equine vet. J.* **18**, 371-374.
- Fruen, B.R., Mickelson, J.R. and Louis, C.F. (1997) Dantrolene inhibition of sarcoplasmic reticulum Ca<sup>2+</sup> release by direct and specific action at skeletal muscle ryanodine receptors. *J. Biol. Chem.* **272**, 26965-26971.
- Harris, P.A. (1991) The equine rhabdomyolysis syndrome in the United Kingdom: epidemiological and clinical descriptive information. *Br. vet. J.* **147**, 373-384.
- Harris, P.A. (1997) Equine rhabdomyolysis syndrome. In: *Current Therapy in Equine Medicine 4*, Ed: N.E. Robinson, W.B. Saunders Co., Philadelphia. pp 115-121.
- Harris, P.A. and Mayhew, I.G. (1998) Musculoskeletal disease. In: *Equine Internal Medicine*, Eds: S.M. Reed and W.M. Bayly, W.B. Saunders Co., Philadelphia. pp 379-382.
- Haverkort-Poels, P.J., Joosten, E.M. and Ruitenbeek, W. (1987) Prevention of recurrent exertional rhabdomyolysis by dantrolene sodium. *Muscle Nerve* **10**, 45-46.
- Hodgson, D.R. (1993) Exercise-associated-myopathy: is calcium the culprit? *Equine vet. J.* **25**, 1-3.
- Hodgson, D.R. and Rose, R.J. (1994) Recurrent exertional rhabdomyolysis. In: *The Athletic Horse: Principles and Practice of Equine Sports Medicine*, W.B. Saunders Co., Philadelphia. pp 171-174
- Jones, W.E. (1989) Exercise intolerance - muscular causes. In: *Equine Sports Medicine*, Lea and Febiger, Philadelphia. pp 262-267.
- Lentz, L.R., Valberg, S.J., Balog, E.M., Mickelson, J.R. and Gallant, E.M. (1999) Abnormal regulation of muscle contraction in horses with recurrent exertional rhabdomyolysis. *Am. J. vet. Res.* **60**, 992-999.
- Lentz, L.R., Valberg, S.J., Herold, L.V., Onan, G.W., Mickelson, J.R. and Gallant, E.M. (2002) Myoplasmic calcium regulation in myotubes from horses with recurrent exertional rhabdomyolysis. *Am. J. vet. Res.* **63**, 1724-1731.
- Lopez, J.R., Rojas, B., Gonzalez, M.A. and Terzic, A. (1995a) Myoplasmic Ca<sup>2+</sup> concentration during exertional rhabdomyolysis. *Lancet* **345**, 424-425.
- Lopez, J.R., Linares, N., Cordovez, G. and Terzic, A. (1995b) Elevated myoplasmic calcium in exercise-induced equine rhabdomyolysis. *Pflugers Arch.* **430**, 293-295.
- MacLeay, J.M., Sorum, S.A., Valberg, S.J., Marsh, W.E. and Sorum, M.D. (1999) Epidemiologic analysis of factors influencing exertional rhabdomyolysis in thoroughbreds. *Am. J. vet. Res.* **60**, 1562-1566.
- McGowan, C.M., Fordham, T. and Christley, R.M. (2002) Incidence and risk factors for exertional rhabdomyolysis in thoroughbred racehorses in the United Kingdom. *Vet. Rec.* **151**, 23-26.

- Rosalki, S.B. (1967) An improved procedure for serum creatinine phosphokinase determination. *J. Lab. clin. Med.* **69**, 696.
- Valberg, S., Jönsson, L., Lindholm, A. and Holmgren, N. (1993) Muscle histopathology and plasma aspartate aminotransferase, creatine kinase and myoglobin changes with exercise in horses with recurrent exertional rhabdomyolysis. *Equine vet. J.* **25**, 11-16.
- Valberg, S.J., Mickelson, J.R., Gallant, E.M., MacLeay, J.M., Lentz, L. and De La Corte, F. (1999) Exertional rhabdomyolysis in Quarter Horses and Thoroughbreds: one syndrome, multiple aetiologies. *Equine vet. J., Suppl.* **30**, 533-538.
- Volfinger, L., Lassourd, V., Michaux, J.M., Braun, J.P. and Toutain, P.L. (1994) Kinetic evaluation of muscle damage during exercise by calculation of amount of creatine kinase released. *Am. J. Physiol.* **266**, 434-441.
- Ward, A., Chaffman, M.O. and Sorkin, E.M. (1986) Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update on its use in muscle spasticity. *Drugs* **32**, 130-168.
- Ward, T.L., Valberg, S.J., Gallant, E.M. and Mickelson, J.R. (2000) Calcium regulation by skeletal muscle membranes of horses with recurrent exertional rhabdomyolysis. *Am. J. vet. Res.* **61**, 242-247.