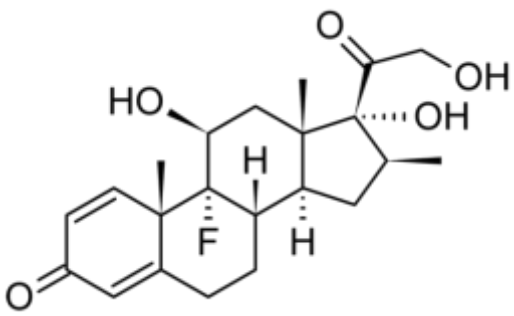
CONTROLLED THERAPEUTIC MEDICATIONS
MONOGRAPH SERIES

Dantrolene

Background

Dantrolene is conventionally used in racehorses as a skeletal muscle relaxant.[i] It is assigned a 4/C by the ARCI. It may be administered prior to strenuous exercise as prophylaxis, or at the onset of clinical signs, as a treatment for exertional rhabdomyolysis, also referred to as tying up.[ii] Dantrolene, as dantrolene sodium, is a prescription medication with FDA approval for use in humans. Indications for human use are conditions associated with upper motor neuron disorders (*e.g.,* cerebral palsy and multiple sclerosis). Dantrolene is commercially available in 25 mg, 50 mg, and 100 mg capsules under the trade name Dantrium™.[iii] In the equine patient, extra-label oral administration is most common as the intravenous product is cost-prohibitive.[iv] Suggested doses for prevention of exertional rhabdomyolysis vary widely, ranging from a 300 mg total dose to 4 mg/kg.[v] Compounded products prescribed for a specific horse may be obtained as a paste or suspension.



"Dantrolene Tanaka et al" by Fvasconcellos (talk · contribs) - Own work, after Tanaka R et al (2004). "Structure of Dantrolene". Analytical Sciences X-ray: Structure Analysis Online 20: x97. doi:10.2116/analscix.20.x97. Licensed under Public Domain via Commons - https://commons.wikimedia.org/wiki/File:Dantrolene_Tanaka_et_al.svg#/media/File:Dantr olene_Tanaka_et_al.svg.png

The mechanism of action by which dantrolene works in horses prone to tying up is poorly understood but may be associated with its ability to decrease calcium release from the sarcoplasmic reticulum within the skeletal muscle. [vi] When used alone, there have been no reports of adverse reactions.

There are several drug interactions which practitioners should be aware of when prescribing or administering dantrolene. The following medications have been associated with an increased risk of adverse reactions when administered in conjunction with dantrolene:

- Benzodiazepines – may cause profound sedation[vii];
- Calcium Channel Blockers – reports in humans of cardiovascular collapse (rare)[viii];
- Estrogen –increase in risk of hepatotoxicity reported in humans[ix];
- Vecuronium – may increase neuromuscular blocking activity[x]; and
- Warfarin – may displace plasma-bound dantrolene increasing effects[xi].

Administration Studies

Oral Administration – Dantrium™ Capsules

Dantrolene, as dantrolene sodium capsules, was administered to eight exercise-conditioned Thoroughbred horses (geldings and mares). The capsules were placed in an oral dose syringe and dissolved in water. The contents were then administered in the back of the horses' mouths. All horses received a one-time 500 mg oral dose of Dantrium™.

Blood samples were obtained immediately before dose administration and at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 hours.

Oral Administration – Compounded Dantrolene Paste

Compounded dantrolene paste (20 mg/mL) was obtained from Wedgewood Compounding Pharmacy (Swedesboro, NJ). The paste was prepared in an oral dosing syringe which was then used to deposit the paste at the back of the horses' mouths. Eight exercise-conditioned Thoroughbred horses (geldings and mares) were administered a one-time 500 mg dose of the compounded dantrolene paste.

Blood samples were obtained immediately before dose administration and at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 hours.

Both administration studies were performed under the direction of Dr. H. Knych at the Maddy Equine Analytical Pharmacology Laboratory, University of California - Davis.

Extraction and Analysis Procedures

Quantification of dantrolene in plasma was performed at the Maddy Equine Analytical Pharmacology Laboratory, University of California - Davis using validated methods similar to those previously described[xii]. Dantrolene was determined in plasma by LC-MS using an internal standard for 5-hydroxyl-dantrolene purchased from Toronto Research Chemicals to improve quantitative accuracy and precision. The LC-MS method for determination 5-hydroxyl-dantrolene in plasma had a limit of quantification (LOQ) of 100 pg/mL and a lower limit of detection (LOD) of 10 pg /mL.

Pharmacokinetic Modeling

Nonlinear least square regression was performed on plasma hydroxyl-dantrolene concentrations using WinNonlin Version 5.2; Pharsight, Cary. 5-hydroxyl-dantrolene data were analyzed via noncompartmental analysis.

Results and Discussion

In all horses, plasma concentrations of the parent drug dantrolene were below the Limit of Quantification (LOQ) by 36 hours and below the Limit of Detection (LOD) by 48 hours after a single oral administration. Average plasma dantrolene concentrations peaked between 4 and 6 hours for both the capsule and paste formulations. Similarly, 5-hydroxyl-dantrolene concentrations, a metabolite of dantrolene, peaked in plasma between 4 and 6 hours, but maximum concentrations were approximately twice that of the parent drug. Researchers therefore elected to further investigate 5-hydroxyl-dantrolene to afford longer detection times. Plasma concentrations of 5-hydroxyl-dantrolene are expressed as the mean, median, and range at the 48-hour collection point (Tables 1.1 and 1.2, adapted from Knych *et al.,* 2010).

Table 1.1 Plasma 5-hydroxyl-dantrolene mean ±SD and median values at recommended withdrawal time following oral administration of 500 mg of dantrolene capsules to 8 horses

Time (hours)	Mean±SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
48	Less than LOQ	Less than LOQ	N/A

Table 1.2 Plasma 5-hydroxyl-dantrolene mean and median values +/- SD at recommended withdrawal time following oral administration of 500 mg of compounded dantrolene paste to 8 horses

Time (hours)	Mean±SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
48	0.04±0.03	0.04	0.0-0.05

Scientific Advisory Committee Recommendation

The 95/95 tolerance interval was calculated using plasma concentration data from the samples collected 48 hours post-administration of a single 500 mg oral dose of dantrolene in eight horses. It resulted in a value of 0.08 ng/mL.

The RMTC Scientific Advisory Committee recommended a regulatory threshold of 100 pg/mL (0.1 ng/mL) of 5-hydroxyl-dantrolene (5-OH dantrolene) in serum or plasma and corresponding withdrawal guidance of 48 hours for a single oral 500 mg dose.

Practice Tips

While dantrolene is available as a compounded product, there is risk in using such products in proximity to a race as there have been multiple instances where the concentration of drug in a compounded formulation differs from that declared on the product label. If dantrolene is to be

administered in relative proximity to a race, the use of the commercial product Dantrium™ represents a potentially more reliable strategy.

Dantrolene is often compounded as a suspension. It is important to remind those administering it to vigorously shake the bottle to evenly distribute the particulate drug within the suspending liquid. If not, early doses may be expected to contain less dantrolene than indicated on the label, while later doses may contain substantially more—and result in risk of a concentration in excess of the threshold in a post-race sample.

Reported doses for dantrolene vary widely, and veterinary practitioners will need to adjust withdrawal intervals in consideration of the dose being administered. The mean terminal half-life (the interval required for the plasma concentration to decrease by ½) for dantrolene, as Dantrium™, is 4.0 hr.[xiii] Therefore, if the dose of dantrolene is doubled from 500 mg to 1000, the withdrawal interval should accordingly be increased by a minimum of one half-life.

With approximately 6 half-lives in a 24-hour period, dantrolene would not be expected to bioaccumulate as a result of once daily dosing. However, if dosing is performed BID there is risk of bioaccumulation and the withdrawal interval should be increased in consideration of the duration of the BID treatments. For horses having received repeated BID oral administrations over an extended period bioaccumulation is likely. It is advisable to submit blood (plasma or serum) to ensure that an appropriate withdrawal interval is used.

References

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[viii] Plumb, Donald C., 2015.

[ix] Plumb, Donald C., 2015.

[x] Plumb, Donald C., 2015.

[xi] Plumb, Donald C., 2015.

[xii] Knych, H.K., *et al.*, J. Vet Pharmacol. Therap. (2010).

[xiii] Knych, H.K., *et al.*, J. Vet Pharmacol. Therap. (2010).