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Dantrolene as a possible prophylactic treatment for *RYR1*-related rhabdomyolysis

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Background

Rhabdomyolysis (RM) may result from gene-environment interactions (1). Mutations in *RYR1* lead to various neuromuscular phenotypes including malignant hyperthermia susceptibility and RM (2, 3). Preventive measures specifically aimed at *RYR1*-related RM mainly consist of avoidance of known triggers such as exercising in hot environments and untreated pyrexia. We report use of oral dantrolene as a prophylactic treatment for *RYR1*-related RM in three severely affected patients (patient consent was obtained for case report publication) (Table 1).

Case Series:

In all patients recurrent RM episodes were characterized by slow evolution of symptoms and gradually rising serum creatine kinase (CK) levels over several days following

exposure to triggers, progressing to abrupt onset of severe muscle breakdown frequently requiring critical care admission. P1, who was asymptomatic in between recurrent episodes of RM, was prescribed 25mg oral dantrolene to take at the symptom onset in an attempt to stop progression to a full RM episode. On follow-up assessment twelve months after treatment initiation, P1 reported occasional dantrolene use to be beneficial, reporting complete abatement of symptoms within 20-30 minutes when dantrolene was taken early after onset of severe myalgia or muscle cramps. He recently had an episode of severe leg pain with rise in CK (4,111 IU/l). At that time he had run out of danrtrolene tablets. Potential triggers were: stress, increased caffeine intake and working in a hot environment. He was re-started on dantrolene 25mg three times daily for two weeks; there was no further rise in CK and his muscle symptoms normalised within a few days. P2 had a history of debilitating daily muscle cramps and high CK on minimal activity for two years following his first episode of acute RM induced by cycling in hot weather. Dantrolene 25mg three times daily was prescribed for two weeks leading to complete resolution of his symptoms; he was able to resume work and had marked improvement of his general quality of life. He was able to resume symptom-free exercise by taking a single dose of 25mg dantrolene prior to physical activity, and has been cycling 45 minutes twice daily (to and from work). Whilst on dantrolene (12 months), neither P1 nor P2 had an RM episode. P3 (II.2 from Family 7 in (2, 4)) started using dantrolene after the second episode of RM at age 15 (CK 378,900 IU/l), at a dose of 25mg two times daily, increasing to four times daily whenever she experiences increased myalgia or cramps. On this treatment regime, over a 6.5-year-period she has suffered four additional episodes of RM, but with less markedly elevated CK levels (varying between 38,860IU/l and 9,738IU/l), not requiring further ICU admissions. All patients reported being more confident to exercise while using dantrolene. None of the patients had dantrolene-related side-effects, with persistently normal liver function tests.

Discussion:

Dantrolene is a muscle relaxant that selectively blocks the RyR1 channel, and its effects on skeletal muscle are mainly related to the inhibition of intracellular calcium release, which plays an important role in skeletal muscle excitation-contraction coupling. Dantrolene has been used for the treatment of malignant hyperthermia, neuroleptic malignant syndrome, spasticity and recently has been reported as a treatment option for chronic muscle pain in a patient with MH susceptibility due to *RYR1* (5). Adverse effects of dantrolene are usually more prominent with long-term treatment, and generally minor compared to a severe and potentially life-threatening RM episode.

We described the intermittent or regular use of dantrolene for the prevention of *RYR1*-related RM, probably one of the most common forms of genetically determined exertional myalgia and RM. In the reported cases, the benefits of dantrolene administration by far outweighed potential associated risks. Limitations of this study are the small sample size (n=3) and the relatively short follow-up period for P1 and P2 (twelve months) compared to P3 (6.5 years).

Dantrolene is very commonly administered orally to (often valuable) rhabdomyolysis-susceptible Thoroughbred racehorses (2 to 3 mg/kg) in training, typically 60-90 minutes prior to exercise: experimental and anecdotal evidence suggests the drug is highly efficacious (6, 7). Whilst an *RYR1*-mutation is unlikely on the basis of linkage analysis in this animal model (8), a calcium-related homeostatic disorder is supported by prior *in vitro* caffeine-contracture experiments (9). Dantrolene reduces sarcoplasmic reticulum calcium release, and lowers resting calcium in cultured equine muscle cells (10), perhaps accounting for its prophylactic efficacy *in vivo* (6, 7). Whilst clinically-detectable side effects following its administration to horses are very rare at recommended doses, higher doses have been associated with short-lived paresis in some animals (11); sub-clinical biochemical effects on hepatic function have

not been reported, despite its worldwide use. Exercise-performance is not knowingly impaired at recommended doses, thereby enabling incremental training programmes to get a horse to full fitness. Typically, the drug is used in RM-susceptible animals, when training levels are increasing in intensity or following a period of rest and its use is withdrawn prior to racing.

This is the first report indicating a role of dantrolene in preventing and/or ameliorating *RYR1*-related RM in humans. Considering the economic impact and quality of life consequences of recurrent RM, we believe that its occasional use to prevent or abort an attack of RM should be further investigated. Undertaking a randomised controlled trial to assess risks and benefits of dantrolene in this group of patients in more detail could help to evaluate the role this drug in preventing *RYR1*-related RM, and, possibly, other genetically determined forms of RM, in particular those related to abnormalities of calcium homeostasis, excitation-contraction coupling and the triad.

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Table 1: *RYR1*-related rhabdomyolysis in three European patients

	Patient 1*	Patient 2*	Patient 3
Gender / Age of onset (Current Age)	Male / 12yrs (18yrs)	Male / 37yrs (40yrs)	Female / 14yrs (22yrs)
RYR1 variant (heterozygous)	c.8054C>T p.(Ser2685Phe)	c.6838G>A p.(Val2280Ile)	c.7300G>A p.(Gly2434Arg)
PolyPhen-2 Prediction (score)	Probably Damaging (0.978)	Possibly Damaging (0.952)	Probably Damaging (0.999)
Previously reported as pathogenic	Novel	Yes	Yes
Freq ExAC	0.000008268 Singleton	0.00003366 <1/10000	0.00002479 <1/10000
Number of RM episodes	Several	Several	Several (six documented)
Number of RM episodes whilst on Dantrolene	None (12 months)	None (12 months)	4 (6.5 years) – CK levels 89-97% lower than before
Triggers for RM	High volumes of Coca Cola or coffee intake, stress/anxiety, exercise, hot ambient temperature	Exercise performed in hot ambient temperature	Strenuous exercise, viral infection, stress/anxiety, lack of sleep
Highest CK / Baseline CK (IU/l)	250,000 / 182	57,000 / 150	378,900 / 164
History of MH	None	None	None
Muscle Biopsy	Minicores	Not Performed	Mild unevenness of oxidative staining
Liver function tests following Dantrolene intake	Normal	Normal	Normal

*: Diagnosed by next generation sequencing; CK: creatine kinase; MH: malignant hyperthermia

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