Category: Advances in the treatment of neuromuscular disorders

Dantrolene as a treatment option for *RYR1*-related rhabdomyolysis

Renata Siciliani Scalco[1,2], Nicol C. Voermans[3], Richard J Piercy[4], Heinz Jungbluth[5,6,7], Ros Quinlivan[1,8]

1) *MRC Centre for Neuromuscular Diseases and Department of Molecular Neuroscience, University College London (UCL) Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK*
2) *CAPES Foundation, Ministry of Education of Brazil, Brasilia, DF, Brazil*
3) *Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands*
4) *Comparative Neuromuscular Diseases Laboratory, Royal Veterinary College, London, UK*
5) *Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London (KCL), London, UK*
6) *Randall Division for Cell and Molecular Biophysics, Muscle Signalling Section, King's College London, London, UK*
7) *Department of Paediatric Neurology, Evelina Children's Hospital, Guy's & St Thomas NHS Foundation Trust, London, UK*
8) *Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London, UK*

Background: Mutations in *RYR1* lead to various neuromuscular phenotypes including rhabdomyolysis (RM). We recently reported the use of oral dantrolene as a prophylactic treatment for *RYR1*-related RM. Here we will report updated data on safety of dantrolene in the reported patients and report the dantrolene use in RM-susceptible thoroughbred racehorses.

Methods: Case series.

Results: Three patients presenting with severe recurrent episodes of *RYR1*-related RM were prescribed 25mg of oral dantrolene up to a maximum of three times a day to be taken as required with symptom onset in order to stop progression of RM episodes. P1 and P2 were on dantrolene for 18 months while P3 continued treatment for 7 years. P1 reported complete abatement of symptoms within 20-30 minutes of taking dantrolene soon after onset of myalgia/cramps. P2 was able to resume symptom-free exercise by taking 25mg of dantrolene prior to physical activity. P3 started using dantrolene after the second episode of RM. Over a 7-year-period she has suffered fewer additional episodes of RM, but with less markedly elevated CK levels. No significant side-effects were reported and the liver function remained normal in all 3 patients.

Dantrolene is highly efficacious for rhabdomyolysis-susceptible Thoroughbred racehorses (2 to 3 mg/kg) in training, administrated orally 60-90 minutes prior to exercise. 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.

Conclusion: Short term intermittent use of low dose dantrolene appeared to be beneficial in three patients with recurrent *RYR1*-related rhabdomyolysis without undue side-effects. Benefits of dantrolene therapy have also been reported in RM-susceptible thoroughbred racehorses. Undertaking a RCT to assess risks and benefits of dantrolene in this group of patients more systematically could help to evaluate the role of Dantrolene in *RYR1*-related RM.