

Idebenone protects against chemotherapy-induced skeletal muscle wasting and mitochondrial dysfunction in mice

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Background: Cancer is the one of the leading causes of death worldwide with 2 in 3 men and 1 in 3 women being diagnosed before the age of 60. Chemotherapy is commonly used as a systemic anti-neoplastic treatment for cancer, but induces a wide variety of serious side-effects that complicate treatment; limit dosage and, therefore, therapeutic efficacy; and severely reduce patient quality of life both during and after treatment. Emerging data from our laboratory (Cheregi *et al.* 2015), and others (Gilliam & St. Clair, 2011), suggests that various chemotherapy agents induce skeletal muscle atrophy and wasting, of which mitochondrial dysfunction and ROS production are key features. Targeting the mitochondria with therapeutic intervention during the course of chemotherapy administration, could therefore, present a novel and effective treatment strategy against the side-effects of anti-cancer therapy. In this study we have investigated the effects of the platinum-based chemotherapeutic agent, Oxaliplatin, on the skeletal musculature (both at the whole body and fibre level) of mice; and the efficacy of the synthetic CoQ10 compound, Idebenone to protect skeletal muscle against chemotherapy-induced side-effects with a focus on mitochondrial metabolism as a precursor.

Method: Animal experimentation was approved by the Victoria University Animal Ethics Experimentation Committee and performed in accordance with the Australian Code of Practice for the Care and use of Animal for Scientific Purposes. In this study, 6 week old, male, Balb/C mice were treated with 6 intraperitoneal injections of Oxaliplatin (3mg/kg/d) over two weeks with and without Idebenone (200mg/kg/d). Prior to, and following the commencement of treatment, whole body metabolism and voluntary exercise capacity were assessed using Promethion metabolic cages (Sabel Systems, USA) for 24 hours. Body composition was also assessed using echoMRI. Thereafter, mice were anaesthetized *via* intraperitoneal injection of sodium pentobarbitone (60mg/kg) and the *flexor digitorum brevis* (FDB) removed. The FDB was triturated to isolate individual fibres and analysed for viability *via* MitoTracker staining and ROS production *via* MitoSox staining (all Molecular Probes).

Results: Oxaliplatin treated mice showed a 10% total body weight reduction and lean muscle mass loss of 20% ($P<0.05$). Oxaliplatin also considerably reduced mitochondrial viability ($P<0.01$) and increased mitochondrial ROS production by ~40% ($P<0.01$). However, concomitant treatment of Idebenone with Oxaliplatin elicited significant protection against reduced mitochondrial viability largely returning it to control levels ($P<0.001$). Concomitant therapy with Idebenone also protected the skeletal musculature against excess mitochondrial ROS production ($P<0.05$) and total body, lean muscle and fat mass loss ($P<0.01$) with co-treatment groups maintaining control levels. No significant difference was observed between the average kilojoules burnt per hour between treatment and/or control groups.

Conclusion: This study is the first to investigate the effects of Oxaliplatin, both alone and in addition to Idebenone co-therapy on the skeletal muscle, and more specifically, mitochondrial viability and function. Our results show that Idebenone protects against Oxaliplatin-induced mitochondrial toxicity and ROS production as well as against lean muscle and fat mass loss. These results suggest that Idebenone could be a useful adjunct treatment against the deleterious side-effects associated with Oxaliplatin treatment, improving patient quality of life and reducing post-treatment co-morbidities.

Cheregi BC, Timpani C, Nurgali K, Hayes A & Rybalka E. (2015). G.P.54 - Chemotherapy-induced mitochondrial respiratory dysfunction, oxidant production and death in healthy skeletal muscle C2C12 myoblast and myotube models. *Neuromusc Disord* **25 Suppl. 2**, S202.

Gilliam LA & St Clair DK. (2011). Chemotherapy-induced weakness and fatigue in skeletal muscle: the role of oxidative stress. *Antiox Redox Signal* **15**, 2543-2563.