Idebenone therapy protects against Oxaliplatin-induced gastrointestinal dysfunction

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Background: Colorectal cancer (CRC) is a leading cause of death worldwide. Oxaliplatin is a first-line anti-neoplastic therapy against CRC, and, although effective at increasing patient survival rates, its use is associated with peripheral neurotoxicity and severe gastrointestinal (GI) side-effects which may persist up to 10 years after cessation of treatment. Mitochondrial dysfunction and oxidative stress has been suggested as an underlying mechanism of oxaliplatin neurotoxicity; however the efficacy of targeted mitochondrial therapies to attenuate oxaliplatin-induced GI side-effects is yet to be explored. Idebenone is a synthetic ubiquinone analogue that has been shown to inhibit lipid peroxidation and interact with the electron transport chain to reduce oxidative damage and stimulate oxidative phosphorylation. We have investigated whether co-administration of Idebenone with oxaliplatin can protect GI function in mice.

Methods: 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 we have investigated the effects of chronic, tri-weekly intraperitoneal oxaliplatin (3mg/kg/d) administration with and without idebenone (200/mg/kg/d) co-treatment, on the colonic motor patterns of Balb/c mice. Mice commenced 2 weeks of chemotherapy ± Idebenone co-treatment from 6 weeks of age, and at 8 weeks of age, were anaesthetized *via* intraperitoneal injection of sodium pentobarbitone (60mg/kg) and the GI tract was removed. The entire colon of each mouse was set up in organ-bath chambers to record motor patterns *in vitro*. The proximal end of the colon was connected to a reservoir containing oxygenated physiological saline to maintain intraluminal pressure. The distal end was attached to an outflow tube that provided a maximum of 2 cm H_2O back-pressure. Organ baths were continuously superfused with oxygenated physiological saline solution. Contractile activity of each segment was recorded with a Logitech Quickcam Pro camera positioned 7-8 cm above the preparation. Videos (2×20min) of each test condition were captured. Recordings were subsequently used to construct spatiotemporal maps and analysis of contractile motor patterns.

Results: Oxaliplatin administration was found to reduce the frequency of propagating colonic contractions (P<0.001), increase the frequency of fragmented non-propagating contractions (P<0.001) and increase the basal diameter of the resting colon (P<0.001), indicative of colonic dysmotility. Co-administration of oxaliplatin with idebenone was found to significantly increase the frequency of propagating (P<0.001) and short (P<0.0001) colonic contractions, whilst reducing the frequency of fragmented non-propagating contractions.

Conclusions: This study is the first to examine the effects of co-therapeutic administration of the anti-oxidant idebenone on colonic motor patterns in oxaliplatin-treated mice. Our results indicate that co-administration of idebenone with oxaliplatin protects against oxaliplatin-induced colonic dysmotility and restores a normal motility pattern. These results suggests that idebenone may be a potential treatment for relieving gastrointestinal side-effects associated with oxaliplatin-treatment, improving both clinical application of oxaliplatin and quality of life amongst CRC patients.