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Pharmacological and nutritional treatment trials in McArdle disease

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A systematic review of evidence for randomised controlled trials using pharmacologic and nutritional therapies in McArdle disease was undertaken. Primary outcome measures included any objective assessment of exercise endurance. Secondary outcome measures included changes in metabolic parameters, subjective measures such as quality of life scores and adverse outcomes. Ten randomised controlled trials were identified. Two trials low dose creatine (60 mg/kg/day) and oral sucrose 75 g prior to exercise demonstrated a positive effect.

Key words: McArdle disease, trials

Background

Recessive mutations in the PYGM gene at 11q13 cause McArdle disease (1). Affected individuals are unable to produce muscle phosphorylase resulting in an inability to mobilise glucose from muscle glycogen stores during anaerobic exercise. Oxidative phosphorylation is also significantly impaired because of a virtual absence of pyruvate leading to an abnormally low substrate flux through the tricarboxylic acid cycle. The effect of this decline in oxidative phosphorylation is a decrease in oxygen consumption to 35-40% of that seen in normal individuals (2) and a disproportionate increase in heart rate and ventilation rate occurs in affected individuals compared with normals (3).

There is considerable variability in the severity of symptoms even in individuals that are homozygous for the same mutation. The reasons are unclear but may include differences in lifestyle including diet, fitness and aerobic capability. Because of the block in glycolytic metabolism, muscle activity occurring after the first few minutes of exercise is highly dependent on alternative energy sources including amino acids and free fatty acids. Research strategies have focussed on increasing the availability of these substrates through either supplementation or dietary modification.

A systematic review of the evidence examining the efficacy of pharmacological or nutritional treatments in improving exercise performance and quality of life in McArdle disease was undertaken (4). Twenty publications relating to the treatment of McArdle disease published between 1966-2005 were identified. Of these, ten fulfilled the criteria for inclusion into a systematic review since they were randomised or quasi randomised controlled trials. Open trials and unblinded single case studies were excluded. The primary outcome measure of the review included any objective assessment of exercise endurance measured over a three month period after treatment. Secondary outcome measures included: metabolic changes, subjective measures such as quality of life scores and adverse events.

Studies

A double blind randomised cross-over trial of oral D-Ribose (15 g made up with 150 ml water) compared with placebo given four times a day for seven days included five McArdle subjects (four male and one female aged 20-60 years) (5). The primary outcome measure was a weekly incremental treadmill test with respiratory gas analysis together with a rating of perceived exertion on a BORG scale (RPP). All five patients completed the study but some developed symptoms of hypoglycaemia and or diarrhoea. The drink itself was found to be too sweet and unpleasant to taste. The study failed to show any normalisation of metabolic parameters or improvement in function, although there was some normalisation of ventilatory response to exercise.

A single-blind controlled trial of glucagon in a single female patient utilised isometric grip strength at maximal effort under ischaemic conditions recorded at 10 second intervals as a means of evaluating efficacy (6). Interventions assessed included subcutaneous saline, subcutaneous glucagon (2 mg) and depot glucagon (2 mg). Subject and investigator were blinded. The endurance to different

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treatment modalities was assessed. There was a trend towards improvement with glucagon which was not statistically significant.

Verapamil was studied in a placebo controlled randomised cross-over trial in three McArdle subjects and eight subjects with myalgia from other causes (7). Treatment was given for six weeks with a two week wash out period. Subjects were asked to keep a pain and activity diary and underwent a weekly walking test and were asked to rate perceived pain on a BORG scale. None of the McArdle patients kept satisfactory diaries, two subjects withdrew from the study because of severe headaches and there was no significant difference between Verapamil and placebo.

At least 80% of the total body pool of vitamin B6 (pyridoxine) is in skeletal muscle bound to phosphorylase as the active form of the vitamin, pyridoxal phosphate, this large pool of vitamin B6 is absent in McArdle disease (8). Pyridoxal phosphate is an important co-factor for a number of enzymes involved in amino acid metabolism, thus the extra demands placed on alternative fuel sources in McArdle disease may make patients more dependent on vitamin B6. A single case study suggested deterioration following withdrawal of vitamin B6 after two years of supplementation (9). A randomised placebo controlled cross-over trial of pyridoxine 50 mg was carried out on ten patients and ten age and sex matched normal controls (Beynon, Quinlivan, Phoenix et al. unpublished data). Treatment or placebo was given for ten weeks with a six week washout period. Outcome measures included erythrocyte AST activity to measure vitamin B6 status and programmed stimulation EMG to assess force generation and fatiguability under ischaemic conditions. There was no significant difference in force generation between placebo and pyridoxine.

Two single uncontrolled case studies suggested an improvement in performance when McArdle patients were fed a high protein diet (10, 11). Two randomised controlled trials attempted to investigate this further. One study investigated immediate and long term effects of oral branched chain amino acids (BCAA) (12). Three McArdle and three control subjects were studied. Assessments included a measure of maximal concentric strength and endurance and urine 3-methylhistidine/creatine ratio. Immediate studies compared oral BCAA (0.3 g/kg) with fasting and 100 g dextrose. Subjects were reassessed after one and two months of oral BCAA. The results showed no immediate or long-term benefit from BCAA. The second study (13) studied six subjects in a single blind study comparing BCAA with placebo. Subjects exercised for 20 minutes on a cycle ergometer at maximal intensity for twenty minutes and serum leucine, isoleucine and valine levels measures. Exercise capacity was worse with BCAAs in 5/6 of the subjects.

Dantrolene sodium is normally used for the prevention and treatment of anaesthetic induced rhabdomyolysis by decreasing calcium flux from the sarcoplasmic reticulum, impairing the initiation of the excitation-contraction coupling mechanism. A positive report of dantrolene sodium in reducing exertional myalgia was described in a single McArdle patient (14). A randomised placebo controlled cross-over trial of dantrolene sodium was undertaken with five McArdle subjects (15). The dose was increased over three days to 50 mg three times a day. The intervention phases lasted six weeks with a four week washout period. Dose dependent side effects were reported including tiredness, somnolence, dizziness and muscle weakness. Performance was assessed by a cycle ergometer test with a RPE. There was no significant benefit with Dantrolene sodium compared with placebo.

Creatine supplementation may increase the availability of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and has been shown to benefit exercise capacity of healthy individuals undergoing resistive training (16) and to increase strength in mitochondrial myopathies (17). Vorgerd performed a cross-over trial of creatine 60 mg/kg/day *vs*. placebo for five weeks in nine McArdle subjects (18). The washout period was 4 weeks. Subjects were asked to keep a fatigue severity scale and static plantar exercise in ischaemic and non-ischaemic conditions was assessed using 31-PMRS. Five of the nine McArdle subjects reported subjective improvement and an increase in the tolerance of workload during ischaemic exercise was found. In a follow-up placebo controlled crossover study 60 mg/kg/day Creatine was compared with 150 mg/kg/day in 19 McArdle subjects using the same outcome measures (19). The symptoms of exercise induced myalgia were significantly worsened with the higher dose of creatine.

Haller and Vissing (20) eloquently demonstrated benefit of intravenous glucose during exercise demonstrating a 20% increase in oxidative capacity. Oral sucrose 75 g was compared with placebo 30-40 minutes before fixed intensity exercise on a cycle ergometer (22). Heart rate, work load and RPE together with biochemical measures included glucose, lactate, pyruvate, ammonia insulin and free fatty acids. Oral sucrose was significantly better than placebo in improving exercise performance.

Conclusion

There are few published randomised controlled trials in McArdle disease. It is not yet possible to recommend any specific treatment for the condition. Low dose creatine afforded a modest benefit in ischaemic exercise in a small number of patients. Oral sucrose prior to planned exercise improved performance, but this is not a suitable intervention for every day living. A major problem of therapeutic studies for McArdle disease is a paucity of subjects. Future clinical trials will need to be multi-centre and probably multi-national. In addition, there is a need

to develop generic outcome measures, including baseline parameters in a large cohort of subjects before such studies can be undertaken. Outcome measures should be developed to reflect the normal lifestyle of patients rather than being measures which provide mechanistic interpretation. These lifestyle related outcome measures should be projected onto a baseline of generic baseline studies, in order that future studies have a common dataset to permit cross comparison.

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