

Effect of Oral Sucrose Shortly Before Exercise on Work Capacity in McArdle Disease

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Background: Oral sucrose (75 g) ingested 40 minutes before exercise improves exercise tolerance in McArdle disease.

Objective: To determine whether a lower dose of sucrose administered closer in time to exercise could have a similar beneficial effect on exercise capacity in patients with McArdle disease.

Design: Placebo-controlled crossover.

Setting: Neuromuscular Research Unit at the Department of Neurology, Rigshospitalet, Copenhagen, Denmark.

Patients: Six patients with biochemically and genetically diagnosed McArdle disease.

Interventions: On separate days, the patients were tested after ingestion of either 75 g of sucrose or a placebo 40 minutes before exercise, or 37 g of sucrose or a placebo 5 minutes before exercise. Patients were blinded to test substances.

Main Outcome Measures: Treatment effectiveness was assessed by monitoring heart rate and perceived exertion during exercise.

Results: Both sucrose treatments dramatically improved exercise tolerance, compared with the placebo. The low-dose, 5-minute sucrose trial had a more sustained effect on exercise capacity than the 40-minute trial. The more sustained effect was probably related to more continuous glucose uptake from the intestine and correspondingly higher circulating glucose levels later during exercise.

Conclusions: This study shows that 37 g of sucrose ingested shortly before exercise has a marked and prolonged effect on exercise tolerance in patients with McArdle disease. This treatment is more convenient for the patients and saves more calories than the currently recommended sucrose treatment.

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IN MCARDLE DISEASE, MUSCLE GLYCOGEN breakdown is blocked because of a myophosphorylase deficiency. Glycogen is the most important fuel for muscle energy metabolism early during exercise and at high exercise intensities. Consequently, oxidative capacity is reduced to about half of normal capacity in the first 5 to 10 minutes of exercise in patients with McArdle disease, and sudden vigorous exercise may trigger muscle contracture and myoglobinuria.¹

The severe oxidative energy crisis early in exercise in McArdle disease is epitomized by the "second wind" phenomenon, which is pathognomic for the condition.^{2,3} It denotes a spontaneous improvement in exercise capacity, usually after 7 to 8 minutes of exercise. The second wind is marked by a large drop in heart rate and perceived exertion, and is attributable to higher extramuscular fuel delivery to contracting muscle that partially

rescues substrate-limited oxidative metabolism.³ The extramuscular fuels (hepatic glucose and fat) are mobilized to a higher extent during exercise in McArdle patients, owing to an exaggerated sympathoadrenal responses to exercise.^{3,4} This extra fuel supply improves maximal oxygen uptake, but it is far from normalized compared with healthy patients, indicating that blood-borne fuels cannot fully compensate for blocked muscle glycogenolysis.³

The initial severe symptoms of exercise intolerance in McArdle disease can be alleviated if patients ingest 75 g of sucrose 40 minutes before exercise.⁴ However, waiting 40 minutes may be inconvenient for the patient, and the high intake of calories may cause weight gain. Some of our patients have reported a beneficial effect of sucrose when it is ingested shortly before exercise. We therefore investigated whether a lower dose of sucrose, ingested just 5 minutes before exercise, can improve exercise capacity in patients with McArdle disease.

METHODS

PATIENTS

We studied 6 patients (5 men and 1 woman) with McArdle disease, with a mean age of 36 years (range, 25-55 years). All patients had lifelong exercise intolerance, and had experienced repeated exercise-induced episodes of muscle cramps. The diagnosis was confirmed biochemically and by DNA analysis.⁵ No patient took any medication.

The ethics committee of Copenhagen approved the study. All patients were informed of the risk and nature of the study and gave written consent to participate.

EXPERIMENTAL PROTOCOL

All patients were studied on 5 separate days from 9 to 10 AM after an overnight fast. On the first day, patients performed an incremental exercise test on a bicycle ergometer to identify their maximal oxidative capacity, and thus to find the constant workload level to use in the treatment studies. The patients were blinded to treatments, but were told that they, in random order, would ingest a 660-mL caffeine-free drink that contained 75 g of sucrose or artificially sweetened placebo 40 minutes before exercise, or would ingest a 330-mL caffeine-free drink that contained 37 g of sucrose or artificially sweetened placebo 5 minutes before exercise. During the trials, the patients cycled for 15 minutes on a pedal rate-independent stationary cycle ergometer (CPE 2000; MedGraphics Cardiorespiratory Diagnostics, St Paul, Minnesota) at a constant workload corresponding to approximately 65% of their maximal oxidative capacity. Perceived exertion was scored every minute, using a visual analog scale (the Borg scale, which on the whole-body scale ranges from 6 [least effort] to 20 [most effort]).⁶ Heart rate was monitored continuously, and blood was drawn periodically for analysis of plasma glucose, lactate, and insulin.

ANALYSIS

Venous blood was sampled in syringes containing 10 μ L of 0.33M EDTA per milliliter of blood, spun in a refrigerated centrifuge, and stored at -20°C until analysis. The blood was analyzed for lactate and plasma glucose on a 2300 STAT Plus Glucose and Lactate Analyzer (YSI Inc, Yellow Springs, Ohio). Insulin was measured by radioimmunoassay.

Values are mean (SD). A *P* value of less than .05 (2-tailed testing) was considered statistically significant. Differences among treatments were assessed by a paired *t* test and, when appropriate, an analysis of variance was applied.

RESULTS

EFFECTS OF SUCROSE ON HEART RATE AND PERCEIVED EXERTION

These results are summarized in **Figure 1**. During all trials, patients cycled at a mean (SD) workload of 48 (5) W. Placebo treatments at 5 and 40 minutes did not differ for any variable. Results from these 2 trials are therefore pooled. With the placebo, heart rate peaked at 147 (8) beats/minute and perceived exertion at 16.7 (1.1) beats/minute in the seventh minute of exercise, followed by a spontaneous second wind. In contrast, ingesting sucrose 40 or 5 minutes before exercise completely abolished the second wind. Heart rate and perceived exer-

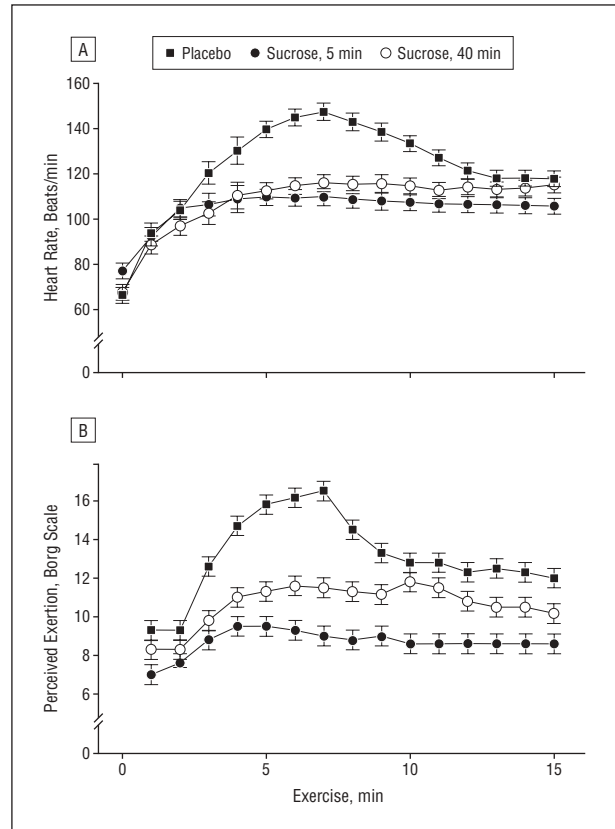


Figure 1. Heart rate (A) and perceived exertion (B) during cycle exercise in 6 overnight fasting patients with McArdle disease who had ingested either a placebo, 75 g of sucrose 40 minutes before exercise, or 37 g of sucrose 5 minutes before exercise. The Borg scale ranges from 6 (least effort) to 20 (most effort). Values are mean (SD).

tion decreased compared with the placebo in the seventh minute of exercise by 32 (5) beats/minute ($P = .02$) and 5.2 (1.0) beats/minute ($P = .009$) in the 40-minute trial, and by 39 (3) beats/minute ($P < .001$) and 7.7 (1.0) beats/minute ($P < .001$) in the 5-minute trial. Perceived exertion and heart rate were consistently lower in the 5-minute trial compared with the 40-minute trial in the second half of the exercise ($P < .05$).

PLASMA LEVELS OF GLUCOSE, LACTATE, AND INSULIN

These results are summarized in **Figure 2**. Pre-exercise ingestion of sucrose improved glucose availability during exercise by 2 mmol/L to 3 mmol/L, compared with the placebo ($P < .001$). Plasma glucose decreased during exercise in the 40-minute trial, but increased in the 5-minute trial, so that plasma glucose levels were higher in the second half of exercise in the 5-minute trial compared with the 40-minute trial ($P < .001$). Plasma lactate levels were higher during exercise in the sucrose group than in the placebo group. Parallel with plasma glucose findings, lactate rose during exercise in the 5-minute trial and decreased in the 40-minute trial.

Both sucrose trials induced hyperinsulinemia, but pre-exercise insulin levels were 300% higher in the 40-minute trial and decreased during exercise, while insulin levels increased in the 5-minute trial.

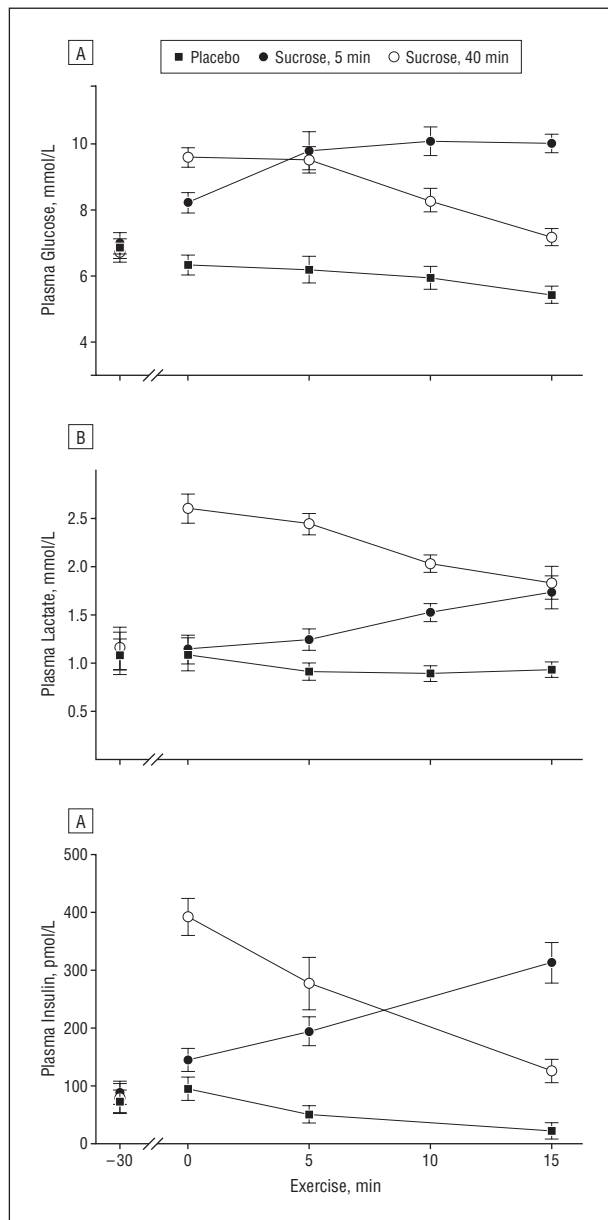


Figure 2. Plasma levels of glucose (A), lactate (B), and insulin (C) during cycle exercise in 6 overnight fasting patients with McArdle disease who had ingested either a placebo, 75 g of sucrose 40 minutes before exercise, or 37 g of sucrose 5 minutes before exercise. Values are mean (SD).

COMMENT

This study shows that ingestion of sucrose 5 minutes before exercise dramatically improves exercise tolerance. It effectively abolished the second wind phenomenon in the first 5 to 10 minutes of exercise in patients with McArdle disease, which is the time window in which patients are particularly prone to muscle necrosis and myoglobinuria. The marked improvement in exercise tolerance is caused by an increased availability of bloodborne glucose, which partially rescues muscle oxidative metabolism early in exercise in myophosphorylase-deficient muscle. The lower dose of sucrose administered shortly before exercise was superior in providing improved exercise tolerance in McArdle patients, com-

pared with administering the double amount of sucrose 40 minutes before exercise. Current recommendations on pre-exercise ingestion of sucrose in McArdle disease³ should therefore be modified.

The goal of our study was to attempt to achieve the benefit of sucrose administration while reducing caloric intake, and to make the treatment more convenient to patients by decreasing the time between sucrose ingestion and exercise. The lower dose of sucrose ingested 5 minutes before exercise also had a more prolonged effect on exercise tolerance, because glucose is continuously absorbed from the gastrointestinal tract, and provides a more sustained elevation in plasma glucose during exercise. These effects were evident in the patients' lower heart rates and ratings of perceived exertion, and in the higher levels of glucose and lactate in plasma observed at the end of exercise in the low dose, 5-minute trial compared with the high dose, 40-minute trial. Both the longer time between exercise and ingestion and the higher dose of sucrose in the 40-minute trial lead to marked hyperinsulinemia.

By eliminating a 40-minute waiting period before exercise, hyperglycemia and hyperinsulinemia at rest can be avoided that would otherwise promote the conversion of absorbed sucrose to fat. Instead, sucrose ingested 5 minutes before exercise is continuously absorbed from the gastrointestinal tract during exercise, and is available for preferential oxidation by contracting muscle. Although this treatment halves the caloric intake, patients should still be cautioned to restrict the use of pre-exercise sucrose to no more than a few times weekly before engaging in strenuous exercise that would otherwise promote contracture and myoglobinuria.

McArdle patients are particularly susceptible to symptoms provoked by static exercise, such as strength training. With this type of exercise, blood supply to the muscle is blocked. While sucrose is thus unlikely to be helpful in static exercise, it is likely to be effective in all kinds of dynamic exercise.

Aerobic conditioning has been shown to increase work capacity, oxygen uptake, and cardiac output in McArdle patients; conversely, physical inactivity can worsen exercise tolerance in the condition.⁷ The adaptations underlying this response are an increase in peak exercise cardiac output, which likely increases the capacity to deliver bloodborne fuels to working muscle, and increased activity of mitochondrial enzymes that enhance the capacity to oxidize available fuels.⁷ Patients may shun aerobic training because of low exercise capacity and susceptibility to exertional muscle fatigue and pain in the first minutes of exercise prior to the onset of a second wind. Pre-exercise sucrose in the initial phase of an exercise training program could potentially help patients to overcome this barrier.

Attempts to boost muscle energy metabolism in McArdle patients by treatment with D-ribose, pyridoxine, creatine, or branched-chain amino acids have failed to improve exercise tolerance,⁸⁻¹¹ and gene therapy is far from being applied to humans.¹² Pre-exercise ingestion of sucrose and aerobic conditioning are therefore currently the most effective treatments presently available for patients with McArdle disease.

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