No effect of triheptanoin in patients with phosphofructokinase deficiency

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**Aim**

Investigate the effect of daily treatment with triheptanoin for 14 days in patients with phosphofructokinase deficiency (PFKD)

**Background**

The deficient enzyme, phosphofructo-1-kinase (PFK), is the rate-limiting enzyme in the glycolytic pathway. Therefore glucose cannot be utilized in muscle energy metabolism.

No pyruvate is generated from the blocked glycogenolysis, thus limiting oxaloacetate production, which is a key intermediate of the TCA cycle.

As a consequence, fat oxidation and ATP production are restricted, which is key for exercise tolerance in patients with PFKD.

Triheptanoin derived C7 may function as a source of anaplerotic substrates for the TCA cycle improving fat oxidation.

**Figure 1:** Proposed principles of triheptanoin treatment in patients with PFKD.
Methods

A randomized, double-blind, placebo-controlled, crossover study.

Outcome measures

Primary:
• Heart rate during submaximal cycle test
• Fatty acid and total oxidation via stable isotope technique and indirect calorimetry

Secondary:
• Glucose and palmitate kinetics
• Perceived exertion (Borg score)
• Exercise measurements
• Self-rated daily function

Participant inclusion criteria

• Diagnosis of PFKD
• Age >15

Demographics:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n:</td>
<td>3</td>
</tr>
<tr>
<td>Age (years) ± SD</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>BMI ± SD</td>
<td>23 ± 5</td>
</tr>
<tr>
<td>Maximal workload ± SD (watt)</td>
<td>44 ± 14</td>
</tr>
<tr>
<td>Submaximal workload ± SD (watt)</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>VO\textsubscript{2}\text{max} ± SD (ml × min\textsuperscript{-1} × kg\textsuperscript{-1})</td>
<td>16 ± 3</td>
</tr>
</tbody>
</table>

Table 1: Demographics and baseline data
BMI, body mass index; VO\textsubscript{2}\text{max}, maximal oxidative capacity
Results

Primary outcomes:
• Triheptanoin did not improve the heart rate during submaximal exercise compared to placebo.
• Palmitate oxidation was increased during submaximal exercise in one patient but did not increase in the two other patients during triheptanoin treatment (figure 4).

Figure 4: Primary outcome measures: Heart rate and palmitate rate of oxidation (Rox) during submaximal to maximal exercise after treatment with triheptanoin ■ and placebo □ for 14 days.

Figure 5: Perceived exertion after treatment with placebo □ and triheptanoin ■ for 14 days. Values are mean of a two minutes interval with standard error of the mean as bars.

Secondary outcomes:
• Mean perceived exertion during submaximal exercise was comparable between treatments (figure 5).
• Palmitate production and palmitate utilization increased during exercise and increased to a greater extent with triheptanoin treatment in all three patients (figure 6).

Figure 6: Palmitate rate of appearance (Ra) and rate of disappearance (Rd), and plasma palmitate concentration submaximal (30 min) to maximal after treatment with placebo ○ and triheptanoin ●. Values are mean with standard error of the mean as bars.

Conclusion

The study indicates that:
• A 14-day triheptanoin treatment does not improve exercise performance, measured as a reduced heart rate or fat metabolism despite increased palmitate production and utilization in patients with PFKD.