1-1-2018

Triheptanoin: A Rescue Therapy for Cardiogenic Shock in Carnitine-acylcarnitine Translocase Deficiency.

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JIMD Reports
DOI 10.1007/8904_2017_36

RESEARCH REPORT

Triheptanoin: A Rescue Therapy for Cardiogenic Shock in Carnitine-acylcarnitine Translocase Deficiency

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Received: 16 March 2017 / Revised: 31 May 2017 / Accepted: 07 June 2017 / Published online: 09 July 2017

Abstract Carnitine-acylcarnitine translocase (CACT) deficiency is a rare long-chain fatty acid oxidation disorder (LC-FAOD) with high mortality due to cardiomyopathy or lethal arrhythmia. Triheptanoin (UX007), an investigational drug composed of synthetic medium odd-chain triglycerides, is a novel therapy in development for LC-FAOD patients. However, cases of its safe and efficacious use to reverse severe heart failure in CACT deficiency are limited. Here, we present a detailed report of an infant with CACT deficiency admitted in metabolic crisis that progressed into severe cardiogenic shock who was successfully treated by triheptanoin. The child was managed, thereafter, on triheptanoin until her death at 3 years of age from a cardiopulmonary arrest in the setting of acute respiratory illness superimposed on chronic hypercarbic respiratory failure.

Communicated by: Manuel Schiff

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Introduction

Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of autosomal recessive inborn errors of metabolism wherein genetic defects in specific mitochondrial enzymes lead to an inability to convert long-chain fatty acids to energy during periods of physiologic stress (Vockley et al. 2017). Amongst the most uncommon fatty acid oxidation disorders, carnitine-acylcarnitine translocase (CACT) deficiency is caused by mutations in *SLC25A20* (Rubio-Gozalbo et al. 2004). CACT is an essential component of the carnitine cycle and is responsible for the importation of long-chain fatty acids from the cytosol into mitochondria for energy production via beta oxidation (Pande and Murthy 1994; Vitoria et al. 2015). Clinical abnormalities occur secondary to energy deprivation and accumulation of potentially toxic long-chain fatty acid intermediates (Rubio-Gozalbo et al. 2004). CACT dysfunction causes hypoketotic hypoglycemia, hyperammonemia, and impairment of fatty acid-dependent tissues, including the heart, liver, and skeletal muscle. Presentation is typically early in life with a relatively severe course, although minor phenotypes have been reported (Pande and Murthy 1994).

Since the first report of CACT deficiency by Stanley and colleagues in 1992, approximately 55 cases have been reported in the medical literature (Stanley et al. 1992; Vitoria et al. 2015). Treatment has focused on dietary modification with frequent, carbohydrate-rich meals, avoidance of fasting, restriction of fat intake, and supplementation with medium chain triglycerides (MCT) (Spiekerkoetter et al. 2009). However, the mortality rate for CACT deficiency remains high (65%), with most deaths occurring in the first year of life due to cardiac complications (Bonnet et al. 1999; Vitoria et al. 2015). The most common cardiac manifestation is cardiomyopathy, but

fatalities are more often reported due to conduction defects and arrhythmias (Bonnet et al. 1999). For patients with CACT deficiency and concomitant cardiac disease, current treatment options are limited to supportive care.

Triheptanoin (UX007) is an investigational drug composed of synthetic medium chain fatty acid which has been used on a compassionate or emergency basis in patients with LC-FAOD and severe cardiomyopathy (Roe and Brunengraber 2015; Vockley et al. 2015, 2016). Here, we present a detailed case of a patient with CACT deficiency and cardiomyopathy devolving into severe cardiogenic shock during a metabolic crisis. With failure of conventional treatments, including MCT and carnitine supplementation, we hypothesized that triheptanoin may arrest further cardiac deterioration and potentially lead to some recovery.

Case Report

The patient is a full-term female born to a 24-year-old G_1P_0 mother with no prenatal or antenatal complications via normal spontaneous vaginal delivery who initially presented with hypoketotic hypoglycemia (glucose 12 mg/dL, ref > 40 mg/dL) and hypothermia (95°F, ref: 97.5–99.3°F) at 23 h of life. Her ammonia and lactate peaked at 319 μmol/L (ref: 64–107 μmol/L) and 4.1 mmol/L (ref < 2 mmol/L), respectively, at 52 h of life. The acylcarnitine profile demonstrated abnormal elevation of numerous long-chain acylcarnitine species, particularly palmitoyl- (16) and oleyl- (C18:1) acylcarnitine, suggestive of carnitine palmitoyltransferase II or CACT deficiency. *SLC25A20* molecular analysis identified compound heterozygosity for a previously reported c.84delT mutation and a 506-kb deletion on chromosome 3p21.31 which includes the *SLC25A20* gene (Eto et al. 2013, Haldeman-Englert et al. 2009, Hsu et al. 2001). On day of life (DOL) 5, she was started on MCT oil to supplement total parenteral nutrition (TPN) and maternal breast milk (MBM). She was discharged on a high MCT formula, maternal breast milk, a carbohydrate module, and additional MCT oil, providing 145 kcal/kg, 1.5 g/kg protein, 33.5% fat calories, 9.5% from long chain fats (LCFA), and 24% from MCT. Of note, her initial echocardiogram (ECHO) at 4 days of age already showed signs of biventricular hypertrophy but with normal systolic function, i.e. left ventricular ejection fraction (EF) 64% and shortening fraction (SF) 41% (ref_{EF}: 49–86%, ref_{SF}: 25–45%). Thus, she was actively followed by the cardiac failure team.

At 5 months, she presented with severe metabolic crisis with hyperammonemia (314 μmol/L) and acute kidney injury (AKI) (creatinine 1.0 mg/dL, ref: 0.2–0.4 mg/dL). By hospital day 3, despite nutritional support with high dextrose-containing TPN, her left ventricular EF and SF had decreased from normal to 33% and 20%, respectively. Her cardiac enzymes rose dramatically with a creatine kinase-MB isoenzyme (CK-MB) of 119 ng/mL (ref < 1.7 ng/mL), troponin of 24 ng/mL (ref < 0.1 ng/mL), and pro-basic natriuretic peptide (pro-BNP) >30,000 pg/mL (ref < 300 pg/mL). Associated arrhythmias (ectopy, diffuse ST changes, left bundle branch block, and QT_c prolongation >550 ms) ensued resulting in cardiogenic shock, necessitating veno-arterial extra-corporal membrane oxygenation (VA-ECMO) for 8 days. Upon recovery from this episode, her cardiac function returned to baseline, i.e. EF 73% and SF 45%. She was discharged on a high MCT formula, infant formula, a carbohydrate module, and additional MCT oil, providing 121 kcal/kg, 1.4 g/kg protein, 37% fat calories, 8.4% from LCFA, and 28.6% from MCT.

At 10 months of age, she suffered another severe metabolic crisis secondary to urinary tract infection and gastroenteritis requiring admission to the pediatric intensive care unit (PICU) for metabolic management and aggressive fluid resuscitation due to moderate dehydration secondary to emesis and diarrhea (stool output up to 30 mL/kg/day in the first 3 days of hospitalization). To provide sufficient calories, total parenteral nutrition (TPN) was started (15% dextrose, 1.2 g/kg amino acids) with continuation of enteral MCT oil, providing 107 kcal/kg/day, MCT providing 21% of total calories. She slowly improved clinically and enteral feedings were initiated on day 5 of hospitalization with gradual advancement to bolus feeds and discontinuation of TPN. She was thereafter transferred to the acute care ward.

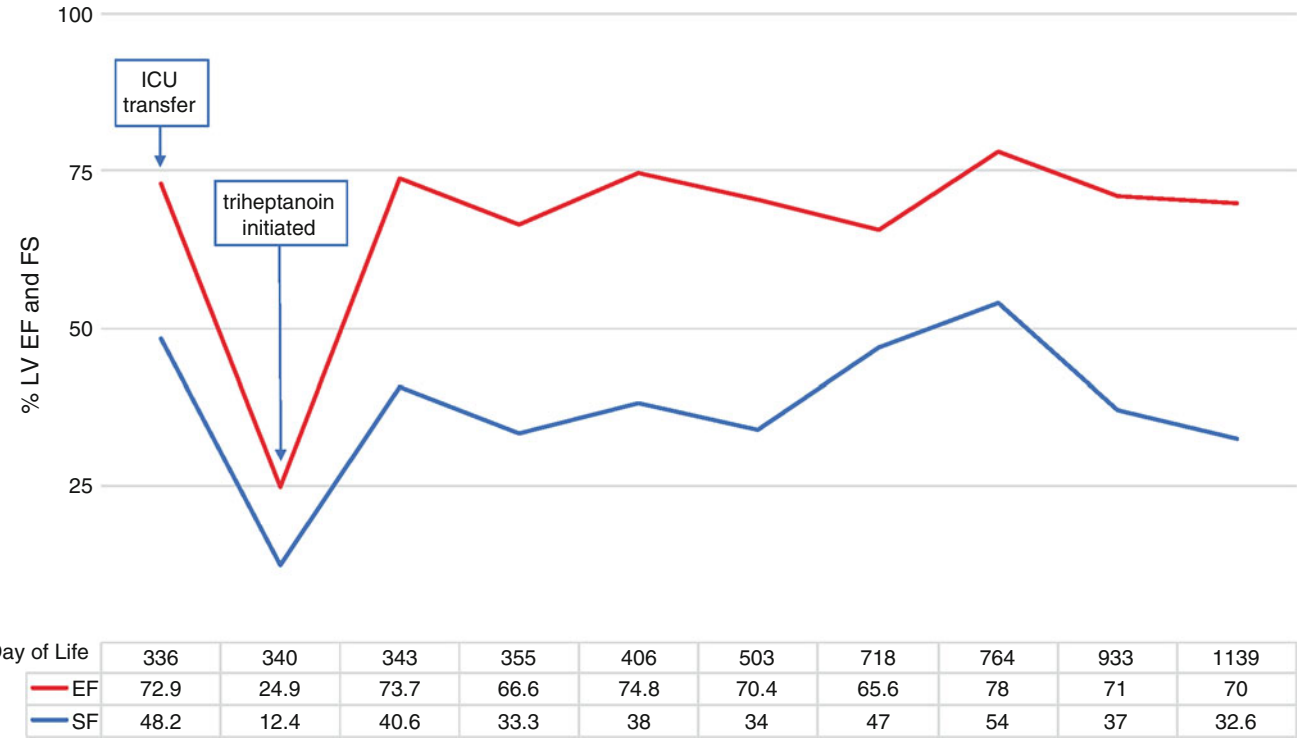
However, on hospital day 8, she was transferred back to the PICU for dehydration from continued diarrhea (stool output >10 mL/kg/day) and oliguric renal failure (creatinine 0.9 mg/dL). Despite appropriate fluid and caloric management (restarted TPN with 10% dextrose, 0.7 g/kg protein, enteral MCT oil, providing 82 kcal/kg/day, with MCT providing 32% of total calories), she developed severe cardiogenic shock within 48 h with extreme tachycardia (>200/min) and hypotension. She had deep ST-depression with elevated cardiac enzymes, i.e. CK-MB and troponin at 97.7 ng/mL and 17.2 ng/mL, respectively. Her pro-BNP was >30,000 pg/mL, lactate peaked at 6.2 mmol/L, and creatinine peaked at 1.2 (Table 1). With myocardial ischemia, a strategy of using multiple low-dose dose vasoactive agents was adopted, including calcium chloride up to 7 mg/kg/h, dopamine up to 7 μg/kg/min, epinephrine up to 0.05 μg/kg/min, and dobutamine up to 7 μg/kg/min, targeting a mean arterial pressure of 50 mmHg, in conjunction with a beta-blocker (esmolol up to 150 μg/kg/min) targeting a heart rate <150/min to optimize cardiac output. She was also started on stress-dose steroids at 50 mg/m^2/day.

Her overall dismal prognosis made her a poor ECMO candidate. On hospital day 13 (EF 24.9%, SF 12.4%, CK-MB 107 ng/mL, troponin 39.9 ng/mL) after obtaining authorization from the Food & Drug Administration (FDA), the Institutional Review Board (IRB), and parental consent,

Table 1 Laboratory test results before and after triheptanoin therapy

	Reference range	Admission to hospital	Transfer to PICU	Cardiogenic shock	Initiation of triheptanoin	After 72 h triheptanoin
Day of hospitalization	–	1	8	10	13	16
Ammonia	<30 μmol/L	143	241	52	40	32
Lactate	<2 mmol/L	0.6	2.8	3.2	1.8	1.9
Creatinine	0.1–0.6 mg/dL	0.4	0.9	1.2	0.9	0.5
Creatinine kinase, total	<250 U/L	N.C.[a]	N.C.	1,990	713	443
Creatinine kinase, MB	<1.7 ng/mL	N.C.	N.C.	97.7	107	24.7
Troponin	<0.1 ng/mL	N.C.	N.C.	17.2	40	7.9

[a] N.C. not checked



Day of Life	336	340	343	355	406	503	718	764	933	1139
EF	72.9	24.9	73.7	66.6	74.8	70.4	65.6	78	71	70
SF	48.2	12.4	40.6	33.3	38	34	47	54	37	32.6

Fig. 1 Cardiac function plotted over time. Prior to and even at admission to ICU, the patient maintained normal biventricular systolic and diastolic function, despite left ventricular hypertrophy. When she suffered cardiogenic shock, ejection fraction (EF) and shortening fraction (SF) both declined precipitously to approximately 25% and 12%, respectively. After 72 h of triheptanoin therapy, her EF and SF returned to baseline. She continued triheptanoin therapy till her death. Prior to death, her cardiac function was close to her baseline

MCT oil was stopped and triheptanoin was initiated via naso-jejunal tube at a dosage of 30 kcal/kg/day (34% of total calories). Three days after initiation of triheptanoin, a repeat ECHO showed normalization of left ventricular EF and SF (Fig. 1) and a >4-fold reduction in cardiac enzymes (Table 1). In the same time frame, all vasoactives were successfully weaned off.

Her enteral diet was advanced to include a very low fat elemental product, infant formula, and a protein module, which, with triheptanoin, provided 90 kcal/kg/day and 1.4 g/kg/day protein with 43% calories from fat, 11% from LCFA, and 32% from triheptanoin. Walnut oil was added as a source of essential fats. She was eventually extubated 18 days after triheptanoin initiation and discharged home a week later. ECHO prior to discharge showed biventricular hypertrophy with good biventricular systolic and diastolic function.

She continued triheptanoin after discharge; dosing was changed to four times a day for ease of administration. Since initiation of triheptanoin, she had two subsequent

admissions, one for hyperammonemia due to acute gastroenteritis and a second for dehydration in the setting of *C. difficile* colitis. During both illnesses, her cardiac function remained stable. At her 20-month clinic visit, she was in overall good health and had developed the ability to sit independently. At 32 months of age, she was diagnosed with obstructive sleep apnea, hypoventilation, hypotonia and hypercarbic respiratory failure requiring noninvasive positive pressure ventilation.

At 3 years of age, she suffered a cardiac arrest precipitated by mucus plugging in the setting of a viral upper respiratory tract infection; care was withdrawn after admission due to devastating neurologic injury. ECHO performed after admission demonstrated no deterioration in function (Fig. 1, day of life 1,139: EF 70%, SF 32.6%). Additionally, her EKGs and rhythm strips showed normal sinus rhythm (NSR).

Discussion

Fatty acid oxidation generates energy during fasting and stress by directly supplying reducing equivalents for mitochondrial oxidative phosphorylation and providing acetyl-CoA to the tricarboxylic acid (TCA) cycle. Loss of this energy source along with impaired ketone body production during metabolic crisis leads to increased demand on the TCA cycle. Medium chain triglycerides are metabolized to the 2-carbon substrate acetyl-CoA that can enter the TCA cycle. In addition to two molecules of acetyl-CoA, triheptanoin provides a 3-carbon propionyl-CoA which can directly enter the TCA cycle as succinyl-CoA through the actions of propionyl-CoA carboxylase and methylmalonyl-CoA mutase (Roe and Mochel 2006). In this manner, triheptanoin provides appropriate substrate balance for the TCA cycle.

Triheptanoin, as treatment for fatty acid oxidation disorders, was first reported in the treatment of three patients with the cardiomyopathic form of very-long-chain acyl-CoA dehydrogenase deficiency (Roe et al. 2002). In these patients, congestive heart failure, rhabdomyolysis, and muscle weakness improved, as did the severity and frequency of metabolic decompensation. Results of a larger series of 20 patients with various long-chain fatty acid oxidation disorders treated with triheptanoin as part of a compassionate use protocol showed significant decreases in mean hospital days per year and hypoglycemia event rates. Of the 12 patients in the series that had cardiomyopathy at the start of triheptanoin therapy, 8 improved, 3 remained stable, and 1 required cardiac transplantation. The single CACT deficiency patient in this cohort had cardiomyopathy that improved, with ejection fraction increasing to 67% from 35% pre-treatment (Vockley et al. 2015). A subsequent case series of ten patients with LC-FAOD and acute heart failure in whom triheptanoin had been initiated for compassionate or emergency use demonstrated return of normal EF within 3 weeks of initiation; only two of these patients had CACT deficiency (Vockley et al. 2016). Now, a single-arm, open-label, multicenter Phase 2 trial has been published demonstrating safety and efficacy in pediatric and adult patients at 24 weeks of treatment; CACT deficiency patients were excluded from this study due to the severity of the condition (Vockley et al. 2017).

Patients with CACT deficiency are at high risk for morbidity and mortality with each fasting period or illness. Despite maximizing supportive measures during a severe metabolic crisis, our patient's condition declined precipitously. Only after providing triheptanoin did cardiac function improve gradually but dramatically, with ejection fraction rising from 24.9 to 73.7%. With continuation of triheptanoin as a routine part of her nutritional management, her cardiac function remained preserved through the next 2 years of life. She even developed the ability to sit independently. Her ultimate death seemed linked to a primary respiratory event rather than a cardiac one. Given the paucity of clinical experience with triheptanoin use specifically in CACT deficiency, our report highlights the safe and efficacious use of triheptanoin in acute heart failure in this subset of patients. Triheptanoin may provide a therapeutic alternative that could potentially lead to improved outcomes for CACT deficiency patients.

Synopsis

This report details the safe use of triheptanoin to reverse cardiogenic shock in the case of a patient with carnitine-acylcarnitine translocase deficiency suffering severe metabolic crisis devolving into acute heart failure.

Compliance with Ethical Guidelines

As the submitting author, I confirm that all authors have adhered to strict ethical guidelines in the generation of this manuscript.

Contributor's Statement

Sidharth Mahapatra contributed to the conception and design of this case presentation, the literature search, drafting the initial manuscript, and revising and reviewing the manuscript.

Amitha Ananth, Nancy Baugh, and Mihaela Damian reviewed and revised the manuscript.

Mihaela Damian contributed to the conception and design of the case presentation and gathered the data to generate the tables and figure.

Gregory Enns contributed to the conception and design of the case presentation, and reviewed and revised the manuscript. He was a member of the UX007 data safety monitoring board.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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