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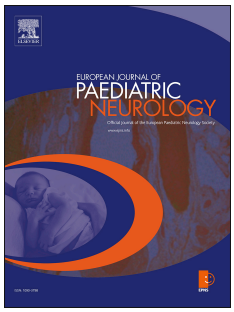

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A pilot study of add-on oral triheptanoin treatment for children with medically refractory epilepsy

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Running headline: triheptanoin for children with medically refractory epilepsy

Abstract

Aim
Despite antiepileptic medication and dietary treatment options available about 45% of children with epilepsy still suffer from uncontrolled seizures. Triheptanoin is an anaplerotic treatment designed to improve energy generation via the Krebs cycle.

Method
For the first time, we evaluated the feasibility, tolerability and efficacy of add-on triheptanoin in 12 patients with medically refractory epilepsy (seven males, five females; min–max: 3–18yr, median 13.5 yr).

Results
Eight out of a total of 12 children (67%), who tested the treatment, finished the trial and tolerated between 30-100 ml of triheptanoin per day for >12 weeks (median 55 ml, 20.5% caloric intake). The most common adverse effects were diarrhoea and other gastro-intestinal effects in seven kids. One child experienced leaking and another child had an infected percutaneous endoscopic gastrostomy button. Five children (62.5%), who all had been on the ketogenic diet previously, showed sustained >50% reductions in seizure frequency, including one patient who became seizure free for 30 weeks. Four patients extended their treatment to a total of 201-909 days, until seizure frequency or severity increased.

Interpretation
In this small trial, triheptanoin was safe and tolerable in children with epilepsy. As some children showed reductions in seizure numbers and/or severity, larger randomised controlled studies are now needed for further evaluation of safety and efficacy.

Highlights:
- Triheptanoin add-on treatment (30-100ml/day) is feasible in children with epilepsy.
- There were mostly non-serious adverse effects, including GI problems (7 of 12 kids).
- Reductions in seizure frequencies in 5 of 8 children (62.5%) during treatment phase.
- Further studies of triheptanoin in epilepsy are warranted.

Introduction
Epilepsy is one of the most common brain disorders in children. Antiepileptic drugs are the first-line treatment options, but they often lead to severe adverse effects including sedation, cognitive dysfunction and psychiatric side effects [1]. Dietary treatment options such as the ketogenic and derived diets are effective in some children [2-5], but the stringent diet regimens are difficult to maintain and can lead to low compliance. Despite many medication and dietary treatment options, about 45% of children with epilepsy still suffer from uncontrolled seizures and about 30% of patients fail to achieve seizure relief from current treatment options [6, 7]. Therefore, alternate treatment options especially those with novel mechanisms of action are warranted.

Triheptanoin is a synthetic medium-chain triglyceride containing seven-carbon heptanoic acid. It is an edible, odorless and tasteless oil which can easily be incorporated into any diet. We have previously established that triheptanoin is neuroprotective and anticonvulsant in several acute and chronic mouse seizure models [8-11]. The anticonvulsant effects of triheptanoin are thought to be attributed to, in large part, anaplerosis, which is the refilling of deficient tricarboxylic acid (TCA) cycle metabolites [10, 12, 13] in the brain.

Triheptanoin is currently being used for the treatment of rare metabolic disorders in children and adults in USA [14-17]. In addition, preliminary studies in humans show that triheptanoin is a potential treatment option for glucose transporter 1 deficiency [18, 19] and Huntington's disease [20]. The effects of triheptanoin in children with epilepsy remain elusive. We hypothesized that triheptanoin will be safe and tolerated in children with epilepsy and will reduce the seizure burden in some children. Here we report the results of our pilot study conducted to assess safety and tolerability of triheptanoin as an add-on treatment for children with treatment-resistant epilepsy.

Methods

This open-label, non-randomized, uncontrolled Phase I study was conducted under the approval of the local Human Research Ethics Committee at the Royal Brisbane Children's Hospital, Lady Cilento Children's Hospital and The University of Queensland. The study was prospectively registered with the Therapeutic Goods Administration and the Australian New Zealand Clinical Trial Registry (ACTRN12614000187640). Written informed consent was obtained from all participants and/or legal guardians prior to the initiation of the study.

Participants

Sixteen children (3 to 18 years old, mean 12 $\pm$ 4 y 6 months) from the paediatric epilepsy clinic at Lady Cilento Children's Hospital were screened to participate in this trial from November 2014 to October 2017. Thereafter, interest into the treatment was lost, as cannabinoids were offered in another trial. Twelve children were enrolled in the study based on the inclusion and exclusion criteria.

Main Inclusion and exclusion criteria

Male or female subjects (3-18 years old) with epilepsy who have experienced at least two motor seizures per fortnight over two months prior to enrolment despite current or prior treatment with at least one AED at clinically appropriate doses were eligible for the trial. Eligible seizure types were complex partial seizures (focal dyscognitive seizures or focal seizures with altered awareness), secondary generalized seizures, simple partial seizures (focal seizures) with motor features, primary generalized seizures, tonic seizures, atonic seizures. There had been no change in anti-epileptic drugs over the four weeks prior to enrolment.

We excluded patients and caregivers with major psychiatric morbidity, history of substance abuse, psychogenic non-epileptic seizures and seizure clusters. We also excluded patients with propionic acidemia or methylmalonic acidemia or with disorders affecting medium and short

chain fatty acid oxidation. This included medium-chain acyl-CoA dehydrogenase deficiency - MCAD, short-chain acyl-CoA dehydrogenase deficiency - SCAD, short-chain-3 hydroxyacyl-CoA dehydrogenase deficiency –SCHAD and HMG CoA (3-hydroxy-3-methyl-glutaryl-CoA) synthase deficiency.

Study design

The timeline of the study is shown in Figure 1. Briefly, all participants were subjected to eight weeks of baseline period during which the number of seizures was counted and only participants with ≥ two seizures per fortnight were enrolled. Recruited participants then underwent a titration period for 3-6 weeks to increase the dosage of triheptanoin oil (Ultragenyx Pharmaceutical Inc., CA, USA) to their best tolerated dose up to a maximum of 35% caloric input or a maximum of 100 mL/day to be distributed over three to five meals per day. During the treatment period of twelve weeks, all participants were required to complete a seizure diary, record adverse events and submit three four-day food diaries. The subjects were monitored for safety with compulsory clinical visits every four weeks during the treatment period. During the final clinical visit, participants were offered to remain on triheptanoin oil for an extension phase if they had benefited from triheptanoin treatment. If extension of treatment was not chosen, the treatment was weaned off over two to four weeks and the participants were examined four weeks later at a final visit. Blood tests were performed at visits 1, 2, 6 and 7 and when necessary to ascertain the health of the subjects.

Statistical analyses

The primary outcome of this study is safety and tolerability of triheptanoin in children with refractory epilepsy measured by the number of adverse events and the number of participants that completed the trial. Secondary outcomes included changes in seizure frequency (minimum 25% change) and number of adverse effects. Since this is a non-randomized and non-placebo controlled pilot study, statistical analysis is not possible and therefore, descriptive statistics are provided for most outcomes. Correlation analysis was performed on changes in caloric intake and changes in body weight using GraphPad Prism 7.0 (GraphPad Software Inc., La Jolla, CA, USA).

Results

Patient cohort, maximal tolerated dose, effects on seizures and compliance

Sixteen children were evaluated to take part in this trial. Twelve children aged 3-18, five girls and eight boys, started to test the effects of triheptanoin (Table 1). Eight children (67%) completed the trial, while four did not. The average dose taken ranged from 30-100 ml, median 55.5 ml (IQR 48.5, 83.25) and the dose taken by those patients who finished the trial was similar, namely 55.5 ml (IQR 48.5-80.5, 95% CI 45-79 ml). The duration of treatment varied from 42 days to 909 days, with a medium of 168 days (IQR 68, 313, **Fig. 2A**).

Out of the eight children completing the trial, five children had improved seizure control, with five children showing reduced seizure frequencies of more than 60%, including one child with additional reductions in seizure severity and another one becoming seizure-free for six weeks. Four of these children went on extensions (see below). Two other boys had initial seizure reduction while on treatment, but unfortunately had later relapses with increased seizures

which led to stopping treatment. On average over the full treatment period, these two boys showed 52% and 56% reductions in seizure frequencies and another girl showed no changes. When seizures recurred, they were still significantly reduced from pre-treatment levels. Unfortunately, seizure diaries were not available for most patients at visit 7 or after off-titration (see below for patients on extension). Therefore we can not provide any numbers on returning seizures frequencies.
The four children enrolled who exited the trial early before visit 4 did not tolerate the drug, in all cases due to gastro-intestinal side effects, such as diarrhea or abdominal pain. In addition, one child did not like taking the drug and the family was not compliant.

Adverse effects
All adverse events are listed in table 2, with the effects that were thought to be related to the drug on the top. Many patients suffered from gastro-intestinal side effects, most commonly diarrhoea, but also vomiting, abdominal pain and constipation, which were resolved. Importantly, in one child a percutaneous endoscopic gastrostomy site was weeping and in another patient the percutaneous endoscopic gastrostomy site became infected, which lead to hospitalization and was reported as a serious adverse event. Two other serious adverse events regarding hospitalization due to increased seizures occurred during the 12 week treatment phase in two other patients, in one case associated with a chest infection.
Other adverse events that were thought to be unrelated to triheptanoin were fever, upper respiratory infection, cough, ingrown toenails, injuries due to falls during seizures, poor sleep, wax in ears and an infection of a bite that occurred during a seizure. The blood levels of valproate and carbamazepine in the patients taking these medications remained within the therapeutic range. No serious interactions with anti-seizure medications were observed during the trial or extension phase, as we did not observe any of the known serious side effects of anti-seizure medication. Regarding changes in body weight in the children, an average of 1 kg gain was found during the treatment phase (range 300 g loss - 4.1 kg increase in body weight, **Fig. 2B**). This includes patient 2 (table 1), a teenager of 180 cm height who gained 4.1 kg and remained healthy.

Changes in eating habits
While taking triheptanoin children increased their caloric intake from baseline levels by 318 Kcal/day (average 19%, range: -12% to 84%, **Fig. 2C**). There is no correlation between reported changes in caloric input and changes in body weight (p=0.68, **Fig. 2D**). To accommodate for the caloric intake of triheptanoin (average of 29%; median 30.5%, 95% CI 22-36%), children reduced the caloric intakes of fats, carbohydrates and proteins by 12%, 11% and 5%, respectively per total caloric intake (**Fig. 2E**).

Previous experience with ketogenic diet
Six children had previously been on ketogenic diets (Table 1). In regards to success on the ketogenic diet, there were either no effects (1 child) or effects wore off (3 children), the child wanted to eat normally (1) or the diet was stopped for unknown reasons (1). Five of these children showed anti-seizure effects while treated with triheptanoin, while one did not tolerate

triheptanoin. Interestingly, children who had not been on ketogenic diets before appeared to tolerate triheptanoin less. Out of the six children who had not been on ketogenic diet before, three children stopped triheptanoin early due to gastro-intestinal side effects. The other three children finished the trial, but did not experience a consistent reduction of seizures.

Extension phase

Four children went on extensions (see table 1, outcome). The following events occurred with the children who have stopped triheptanoin after extending the treatment beyond the 12 week treatment phase.

Participant 1 (16F) went into a 1 month extension phase, during which she had a hypernatremic episode secondary to pan hypopituitarism and status epilepticus. In addition there were problems with compliance and the patient was lost for follow up.

Participant 2 (15M) who continued triheptanoin via a compassionate access scheme was continuously improving with about 1-2 seizure free days per week and typically only one seizure per day until day 780, while before treatment he regularly suffered from 5-10 seizures daily. He then was referred to adult care and stopped taking triheptanoin due to returning atonic seizures. In total, he was taking 100 ml triheptanoin for 2.5 years.

Participant 3 (9M) became seizure-free with 48 ml triheptanoin within the treatment phase. The treatment was extended for 5 additional months and he was seizure-free for 30 weeks in total, until seizures returned to the baseline level of about 3 seizures per week.

Participant 4 (7M) showed 65% reduction in seizure frequency during the 12 week treatment phase and went into extension phase with 55 ml triheptanoin for 1 year until seizures returned.

Discussion

Triheptanoin has been shown to be a potentially effective treatment for some rare metabolic disorders [14-16, 21], suggesting that triheptanoin could be safe and tolerable for long term usage in humans. Here, we described the first study which evaluated the safety and tolerability of triheptanoin as an add-on treatment in a small number of children with refractory epilepsy. The main findings in this study were that children tolerated between 30-100 ml of triheptanoin per day and that adverse effects were mostly limited to gastro-intestinal effects, but also problems with endoscopic gastrostomy buttons. Out of the eight patients who finished the trial, five (62.5%) showed >50% reductions in seizure frequency, including one patient who became seizure free for a period of time. Seizures eventually returned in all patients and reasons were unknown. Additionally, there were no serious interactions with anti-epileptic medications during the trial or extension phase. This indicates that triheptanoin could be safe as an add-on treatment to existing anti-seizure medications.

The ketogenic and derived diets are effective in some children [2-4], but the stringent diet regimens are difficult to comply with for the caregivers. In our experience, this limits the extensive use of the ketogenic diets to few families willing and able to follow stringent instructions. This new treatment approach is simpler than the ketogenic diets especially for the caregivers, since triheptanoin can easily be added to meals or drinks and does not require therapeutic drug monitoring or other forms of close supervision. However, avoidance of gastro-

intestinal side effects with triheptanoin was found to be challenging for some caregivers and patients. For the patients, it is important that triheptanoin is less restrictive than a ketogenic diet.

At this time it is difficult to compare the effects of triheptanoin to ketogenic diets in patients, as the ketogenic diet has been optimized for over 40 years, while this pilot study is the first study of triheptanoin in children with different types of epilepsy. Gastrointestinal side effects with triheptanoin occurred more often when children were sick. The gastro-intestinal side effects were also found in a recent phase II trial for long-chain fatty acid disorders [17] and can be largely managed by slow up titration and mixing triheptanoin with food. Great care needs to be taken in children with percutaneous endoscopic gastrostomy buttons. The reported ketogenic diet's side effects of hunger or lack of energy by Neal et al[2] were not seen in our patients. It is of interest that all patients who were cared for by parents who had previously administered the ketogenic diet finished the treatment and showed less gastrointestinal side effects. It is likely that these parents were more compliant in following instructions, such as slow up titration of the oil and mixing it with food which limits gastrointestinal side effects. This indicates that similar to the ketogenic diet triheptanoin treatment requires vigilance of the caregivers.

Other adverse effects during the triheptanoin treatment phase were minor. Minimal changes in eating habits were observed and the slight increases in caloric intake and body weight were not of concern as children maintained healthy body weights. The reported caloric intake did not correlate with the slight body weight changes during the treatment phase (**Fig. 2D**).

Interestingly, children who had been on ketogenic diets before appeared to tolerate triheptanoin better and had better seizure control than those who had not. It is possible that the families who were able to follow the strict ketogenic diet were more compliant with the prescribed triheptanoin treatment.

Upon ingestion, triheptanoin is broken down into glycerol and heptanoate. Heptanoate can enter the brain directly or is metabolized into C_5-ketone bodies in the liver, namely β-hydroxypentanoate and β-ketopentanoate which are then exported to the blood and other organs [22]. Unlike even-chain fatty acids, β-oxidation of heptanoate produces acetyl-CoA and propionyl-CoA. Propionyl-CoA is able to replenish the TCA cycle through propionyl-CoA carboxylation pathway to produce succinyl-CoA [23]. This is supported by previous studies in the chronic mouse pilocarpine epilepsy model, which found that triheptanoin restored the levels of acetyl-CoA, propionyl-CoA and β-hydroxypentanoate in the brain [10, 12]. The anaplerotic properties of triheptanoin are expected to enhance TCA cycling and consequently ATP production to meet the high metabolic demand in the epileptic brain.

In conclusion, triheptanoin may be a novel treatment option for refractory epilepsy due to its unique metabolic properties. It appears to be a viable treatment for some children with medically refractory epilepsy, especially when caregivers cannot comply with ketogenic diets, although great care needs to be taken to mix triheptanoin with food to avoid gastro-intestinal side effects. Triheptanoin showed promising efficacy in some of the children who completed the trial and went on extension treatment, although eventually all participants showed increases in at least some seizure types within 30 days to about 2.5 years.

Based on the limited number of patients in this trial, further studies are needed to investigate the efficacy and the long-term tolerability of triheptanoin.

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Conflicts of Interest
KB applied for a patent regarding the use of triheptanoin for seizure disorders, which has been licensed to Ultragenyx Pharmaceutical Inc.. Ultragenyx Pharmaceutical Inc. also funded part of the study. The other authors do not have any conflicts of interests.

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Figure legends

Fig. 1 Timeline of the study. The baseline, titration and treatment periods are shown in weeks (w). At all required visits, seizure frequency and severity, eating habits, caloric intake, body weight, AED levels, side effects (Paediatric Epilepsy Side Effects Questionnaire), general and neurological health were assessed. Seizure frequencies were compared at visit 6 vs. visit 2.

Fig. 2 Duration of triheptanoin treatment, changes in body weight, caloric intake and macronutrient composition at end of treatment phase. A The total duration of triheptanoin treatment for each child with refractory epilepsy is shown. The expected end of treatment is inbeetween the two dotted lines. Patients who dropped out early are on the left and patients who extended treatment are on the right of the dotted lines. B The changes in body weight (kg) between visit 6 and visit 2 are shown. None of the changes were of any concern. C The change in % reported caloric intake between visit 6 and 2 are shown in % relative to intake at baseline (visit 2). C Changes of reported caloric intake are plotted against changes in body weight. There was no correlation (n.s. – not significant, p=0.68). E. The macronutrient distribution at the end of the treatment period is depicted. Triangles in different colors indicate the % of caloric intake (IQRs are given within) relative to the total caloric intake (n=8 patients).

	age M/F	Diagnosis	KD [a]	Seizure types	Outcome	Days on drug	Ongoing AEDs (+ rescue)	Dose (ml)	Seizures/ week baseline	% Reduction in seizure frequency [b]	Number of "causal" adverse effects
1	16F	Right parietal arachnoid cyst, brain malformation	yes	1A, C, D	Seizure reduction, 30 day extension until hypernatremia and SE due to hypopituitarism	200	TOP, LEV, RUF, (MID)	50	~ 11	60%	0
2	15M	Epilepsy, intellectual disability	yes	1A-F	Seizure severity reduced, 750 days extension until seizures returned	909	LAC, ZON, CBZ	100	~50	70%	1
3	9M	Epilepsy, CP	yes	1A,C	About 30 weeks seizure free, 200 days extension until seizures returned	339	TOP, LAM, CBZ	48	3.3	100%	2
4	7M	Refractory Epilepsy, global developmental delay, CP	yes	1A, C, E, 2	Seizure reduction, 320 days extension until seizures returned during sickness	433	OXC, LEV, TOP, PHE, CLON, VAL, (MID)	55	1.75	65%	1
5	3F	Epileptic Encephalopathy	yes	1A,C, E, 2	Seizure reduction	168	LAC, ZON	40	48	85%	7
6	7F	Epilepsy, KLEEFSTRA syndrome	no	1A-E	No change	164	VAL, CLON, TOP	56	4.3	0	3 [c]
7	16M	Refractory Epilepsy, ASD, intellectual disability	no	1A-E, 3	Only initial seizure frequency reduction	175	LAM, LAC, RUF	64	5	52%	0
8	14M	Dravet syndrome	no	1A, B	Only initial seizure frequency reduction	164	VAL, STIR, TOP, CBZ, (MID)	86	6.6	56%	3
9	11F	Myoclonic absence epilepsy	no	1E, F	GI side effects	42	VAL, LAM	75	35-67 daily	ND	0
10	13M	Ganglioma, 2^{ndary} symptomatic focal epilepsy	no	1E	GI side effects	63	OXC, LEV	50	1.7	ND	6
11	18F	Frontal cortical dysplasia	no	1D,3	GI side effects	69	CLON, LAM, VAL (MID)	100	23.3	ND	2
12	14M	Dravet syndrome, cerebellar atrophy, intellectual impairment	yes	1A, B	GI side effects, brighter	63		30-60	28	ND	2

Table 1: Patient characteristics and effects of treatment

[a] patients who previously were on ketogenic diet are noted. The ketogenic diet (KD) either did not work or anti-seizure effects wore off. [b] reduction in seizure frequency during 12 week treatment phase in this trial. [c] infected percutaneous endoscopic gastrostomy site.

Seizure types: 1 generalized seizures: A – tonic – clonic, B- clonic, C- tonic, D – atonic, E – absence, F- myoclonic, 2 focal seizures: A evolving into bilateral convulsive seizure, 3 – unknown seizure type (unable to characterize).

Abbreviations: AED – anti-epileptic drugs, CBZ- Clobazam, CLON – clonazepam, CP – cerebral palsy, LAC lacosamide, LAM – lamotrigine, LEV – levetiracetam, MID - midazolam, OXC – oxcarbazepine, PEG – percutaneous endoscopic gastrostomy, PHE – phenobarbitone, RUF – rufinamide, STIR- stiripentol, TOP – topiramate, VAL- valproate, ZON – zonisamide.

Adverse effects	No of patients affected (n=12 total)
Likely causally related to treatment	
diarrhea	7
constipation	2
abdominal pain	2
vomiting	3
anorexia	1
weeping PEG, infected PEG	2
acne	1
none	3
Unlikely causally related to treatment	
fever	2
cough	1
ingrown toe nail	1
poor sleep	1
epistaxis	1
wax in ears	1
rash	1
ear Infection, runny nose	1
post vaccination cough, fever, lethargy	1
sleepy/drowsy	1
infection of a bite (bite occurred during seizure)	1
urinary tract infection	1

Table 2: Number of patients with adverse events likely and unlikely to be related to treatment.

Abbreviations: PEG - percutaneous endoscopic gastrostomy button

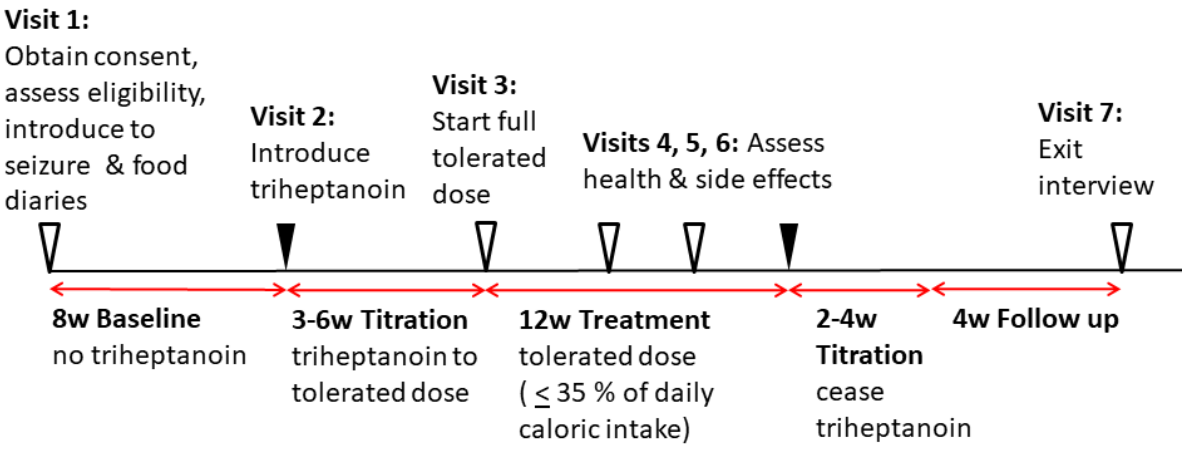
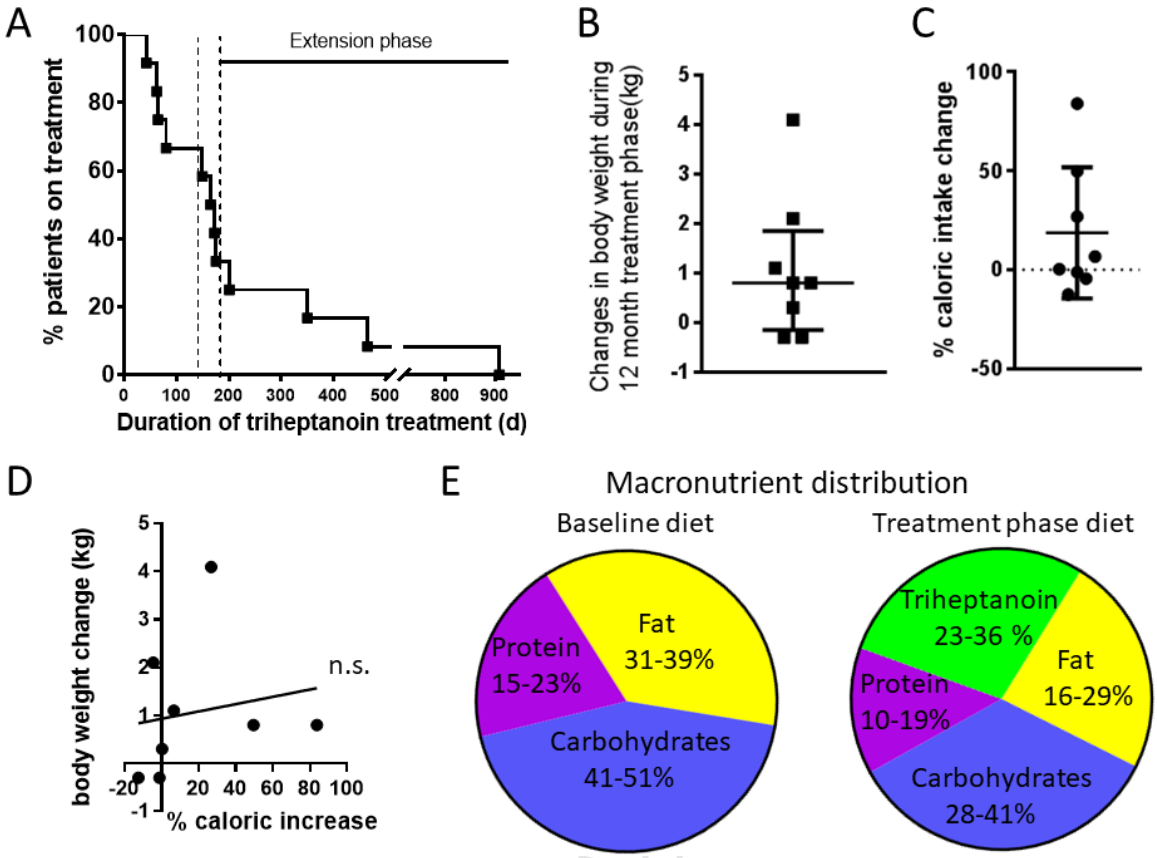


Fig 2



Highlights:

- Triheptanoin add-on treatment (30-100ml/day) is feasible in children with epilepsy.
- There were mostly non-serious adverse effects, including GI problems (7 of 12 kids).
- Reductions in seizure frequencies in 5 of 8 children (62.5%) during treatment phase.
- Further studies of triheptanoin in epilepsy are warranted.