Approved and new dietary options for the treatment of refractory epilepsy

Yvette McMurtrie, Client Services Coordinator, Epilepsy Queensland, Brisbane

Karin Borges, PhD; Lecturer, The University of Queensland, Brisbane; k.borges@uq.edu.au

The majority of people with epilepsy become seizure free with antiepileptic medications or at least find some relief from seizures. However, about 20-30% of people with epilepsy will have treatment-resistant epilepsy, meaning that there is no change in seizure frequency or severity, despite taking anti-epileptic medication. This article describes current dietary therapies available for children and adults with epilepsy and a novel dietary approach in clinical trial.

Ketogenic Diet

The Ketogenic Diet was originally developed in the USA in the early 1920s and has recently been shown to be effective in a randomised clinical trial in children with treatment-resistant epilepsy (Neal et al., 2009). It is a highly restricted dietary regimen that is typically initiated in a hospital. The diet requires careful weighing of foods and is very high in fat, but restricts carbohydrates, protein and caloric intake. Figure 1 compares the Ketogenic Diet to normal diet in terms of the caloric contents of the different fuel components. The Ketogenic Diet is now considered to be the recommended first treatment for specific types of epilepsy in children. Also, it is becoming an important alternative to drug therapy for children with medically intractable seizures. However, it is important to consider that the Ketogenic Diet requires a high level of dietary supervision, commitment and resources. Unfortunately, when attempted in adults, they are not able to adhere to the extreme dietary restrictions of the Ketogenic Diet for a prolonged time period, even when a benefit is seen.

Modified Atkins Diet

In an attempt to create a more palatable and less restrictive dietary treatment, the Modified Atkins Diet was developed in 2003 to treat intractable or refractory epilepsy (Kossoff et al., 2008). The Modified Atkins Diet does not restrict energy, protein or fluid and can be initiated without hospital stay. It is suitable for both children and adults. Kossoff et al. (2008) suggest the following protocol. Daily carbohydrates are limited initially to 10 g/day in children with planned increase after one month to 15 g/day, then 20-30 g/day as tolerated based on seizure control. Adults are started on 15 g/day and can be increased to 20-30g/day after one month. A high fat intake is encouraged, but fasting or food weighing is not required. The ratios of energy coming from different nutrients in the Ketogenic and Modified Atkins Diets are outlined in figure 1. There have been over a dozen studies published on the efficacy of the Modified Atkins Diet since 2006 as well as a randomised controlled trial. On average about 50% of patients experienced greater than 50% seizure reduction and 15-30% of patients experienced greater than 90% seizure reduction (Sharma et al., 2013).

In most cases where dietary treatments are being considered, the Modified Atkins Diet is now used as the first option. This is because it shows similar efficacy rates to the Ketogenic Diet, yet has better tolerability, adherence and fewer side effects. It is more palatable and less restrictive than the Ketogenic Diet and can be administered with fewer resources. Email administration of the Modified Atkins Diet to adults with refractory epilepsy without “face-to-face” dietician support was feasible, safe and effective (Cervenka et al., 2012).

Both the Modified Atkins and Ketogenic Diet cannot be considered a ‘natural treatment’. They have side effects like any medication. Although a varied diet can be provided within the requirements, both are still very limiting on lifestyle. For this reason dietary therapy should only be considered for drug resistant epilepsy, that is, after two appropriate medications have failed. Even though results for Modified Atkins and the Ketogenic Diet are good, very few patients achieve complete long term seizure freedom.
Triheptanoin

A novel metabolic approach to reduce seizures has recently been found to be effective in animal models of epilepsy and seizures. It is currently being tested in adult epilepsy patients at the Royal Melbourne Hospital and children with epilepsy due to glucose transporter 1 (GLUT1) deficiency in the US. The Royal Melbourne Hospital is looking for patients of 16 years or older with treatment-resistant seizures to participate in the trial.

Triheptanoin treatment was developed based on the assumption that energy metabolism is deficient in “epileptic brain tissue” and that the nerve cells cannot produce enough ATP (basic cellular fuel) to maintain a stable membrane potential. Energy-deficient cells are prone to depolarise and subsequently initiate seizures. There is now increasing evidence that there truly is a lack of energy in “epileptic tissue” from epilepsy patients and certain animal epilepsy models (Borges and Sonnewald, 2012; Kovac et al., 2013). Patients with disorders of fat metabolism appear to have similar problems in energy metabolism. To address their energy shortage, triheptanoin (triglyceride of heptanoate, a seven carbon fatty acid) oil can be added to the diet and symptoms largely improve. Children and adults with these fat metabolism disorders tolerate the oil well (Brunengraber and Roe, 2006, Roe and Mochel, 2006) and so far there have been no severe adverse events attributed to triheptanoin.

Triheptanoin is a synthetic, stable and tasteless oil, which currently is not commercially available. When added to a “regular” mouse diet, it reduced the susceptibility to seizures, as well as spontaneous seizures in four different mouse seizure models (Willis et al., 2010, Thomas et al., 2012, Kim et al., 2013). For the mouse studies, 35% of the caloric energy content was provided as triheptanoin, which related to 17g of oil per 100g mouse diet. The clinical trial at Royal Melbourne Hospital aims to find out how much triheptanoin oil can be tolerated by people with epilepsy when added to a normal diet and if seizures can be reduced. Because mice have a higher energy metabolism than people, it is expected that less than 35% of caloric intake of triheptanoin may be beneficial for people with epilepsy. This might equate to about 30-60 ml of oil per day added to normal diet, depending on how much oil can be tolerated and how much food is eaten per day. Patients enrolled into this clinical trial receive counselling and support from a registered and skilled dietician and nurse. They are taught how to eat healthy and how to incorporate triheptanoin into their regular and/or preferred foods. If effective, triheptanoin treatment would be ideal for patients with epilepsy in the developed and developing world, because: 1) triheptanoin does not require refrigeration and is straightforward to add to meals and 2) it is not expected to change metabolism of other drugs and require “drug monitoring” nor to have significant side effects if added to food.

Triheptanoin belongs to the medium chain triglycerides (MCTs), because it contains three 7 carbon long fatty acids (heptanoate) attached to a glycerol backbone (Fig. 2). MCTs are oils containing medium length fatty acids (between 6 and 12 carbons), as opposed to long chain fatty acids that are mostly found in our natural diet, such as vegetable oils and animal-derived fats (14-20 carbons). Naturally MCTs are found in coconut oil. MCT oil, mostly containing 8 and 10 carbon fatty acids, is available in pharmacies and as a sport supplement. It is used to provide fast energy in athletes and patients with (long chain) fat absorption problems or patients who are unable to eat. MCTs can also constitute part of the Ketogenic Diet. Alternatively, in the “pure” MCT Ketogenic Diet, 50-60% of the daily energy intake is in the form of MCTs. When ingested as pure oil, MCT oils often lead to abdominal pain, but mixed into meals or drinks they are much better tolerated. MCTs are now also available in powdered form, e.g. in products for patients on Ketogenic Diet, patients with fat absorption problems or as a treatment for mild Alzheimer’s disease. The powder can be dissolved in drinks or added to meals.

Natural fats and commercially available MCT oils mostly contain even chained fatty acids. When metabolised these provide two-carbon fragments (acetyl-CoA, Fig. 3) to the Krebs cycle in the mitochondria, the powerhouses of cells. This cycle, also called tricarboxylic cycle and citric acid cycle, provides most of the ATP to cells in aerobic metabolism and in the brain. There is evidence that the Krebs cycle does not run efficiently in some “epileptic tissue”. Heptanoate, the main “active” ingredient of triheptanoin, is thought to boost the activity of the Krebs cycle by providing succinyl-CoA to the cycle (Fig. 3). This boosting allows more efficient metabolism of fuels like
medium chain fats and glucose and results in increased ATP production. ATP is required to stabilise the membrane potential in nerve cells, which is important to prevent seizure generation. This mechanism is in contrast to the Ketogenic and Modified Atkins Diet, which provide alternative fuels, namely ketones, but do not boost the Krebs cycle. It is hoped that patients who do not benefit from the Ketogenic or Modified Atkins Diet can achieve seizure relief with triheptanoin.

**Conclusion**

The current dietary options, the Modified Atkins and Ketogenic Diet, are effective to treat seizures in individuals who can adhere to the relatively strict regimens. However, both diets require medical supervision and restrict daily food. Also, even though results for Modified Atkins and the Ketogenic Diet are good, few patients achieve complete long term seizure freedom.

Simpler and effective dietary options for the treatment of epilepsy are urgently needed. Triheptanoin is a novel approach, which would be more straightforward to include into a “normal” diet. It is now important to find out if triheptanoin is tolerated by patients with epilepsy and the extent to which some patients can achieve better control of seizures. Based on the clinical studies in Melbourne and the US, larger clinical studies can be initiated in the future to find out which types of epilepsy best respond to treatment with this novel oil.

**Conflict of interest:** KB has applied for a US patent for the use of triheptanoin as a treatment for epilepsy and together with Professor Terence O’Brien directs the clinical study at the Royal Melbourne Hospital. YM has no conflicts of interests. Research into the use of triheptanoin has been funded by the Australian National Health and Research Council, Citizen United for Research in Epilepsy, The Epilepsy Therapy Project, Parents Against Childhood Epilepsy and the American Epilepsy Foundation (grants to KB).

Patients interested in the clinical trial of triheptanoin at the Royal Melbourne Hospital can contact: Jack Germaine at 03 9342-7879 or email Jack.Germaine@mh.org.au. Patients interested in the Modified Atkins Diet should contact their doctor or doctors at the Royal Melbourne Hospital. A Ketogenic Diet program is available for children at Melbourne’s Royal Children’s Hospital, but waiting lists are long.
Figure 1: Diet options for treatment of epilepsy compared to a normal Western diet

Percent of caloric intake as (long chain) fat, protein and carbohydrate is shown.

Fig. 2 Chemical structure of triheptanoin
The Krebs cycle is responsible for the most ATP production from natural foods in aerobic metabolism. There is evidence that this cycle does not run efficiently in “epileptic tissue”, leading to a shortage of ATP, resulting in instability of neuronal membrane potentials, which will ultimately promote seizure generation. Triheptanoin is thought to boost Krebs cycle activity and ATP production by providing succinyl-CoA, an intermediate of the cycle. By increasing succinyl-CoA production, more acetyl-CoA from other fuels (such as sugar) can be metabolised and produce ATP to stabilize brain activity. Abbreviation: OAA - oxaloacetate

**References**


