

## NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

# Triheptanoin May Mimic Effects Of Anticonvulsive Diet

Researchers working on ways to duplicate the anticonvulsant effects of the ketogenic diet in patients with drug-resistant epilepsy have found that a diet containing a large amount of the triglyceride triheptanoin significantly reduced susceptibility to chronic seizures in two separate mouse models of epilepsy.

But the triglyceride, which has been used to treat hereditary metabolic disorders, did not appear to have an effect on the level of particular citric acid cycle intermediates and metabolites in the brain, Sarah Willis of Texas Tech University and her colleagues reported (*Neurobiol. Dis.* 2010;40:565-72).

When mice were fed a diet containing 35% triheptanoin for 3 weeks before undergoing seizure induction via corneal kindling, the compound delayed the development of kindled seizures, in comparison with mice that were fed a standard diet.

Triheptanoin replaced sucrose and some of the complex carbohydrates that are con-

tained in the standard diet. Elimination of sucrose altogether or use of a 20% triheptanoin diet had nonsignificant effects.

However, if a 35% triheptanoin diet was introduced after the mice became fully kindled, the compound had no effect on seizure severity.

When Ms. Willis and her associates tried the diet in another group of mice 2 weeks after the animals were given pilocarpine to induce status epilepticus (SE), triheptanoin halved the susceptibility of the mice to tonic extension seizures that were induced with an injection of pentylenetetrazole (PTZ). They observed similar reductions in susceptibility to tonic extension seizures when the diet was initiated immediately after pilocarpine.

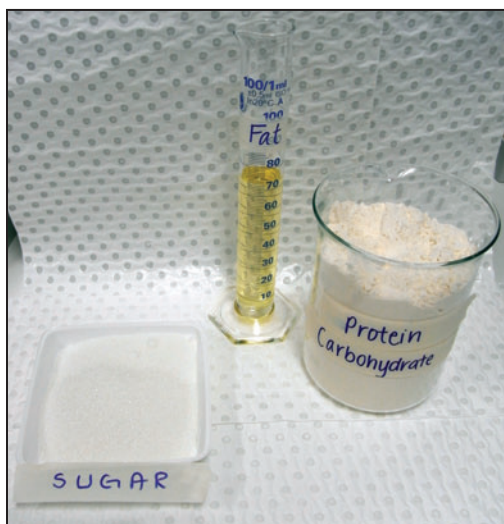
SE mice that were given the standard diet 2 weeks after receiving pilocarpine had significant changes in the brain levels of particular citric acid cycle metabolites (including acetyl-CoA), as well as the neurotransmitters aspartate and gamma-aminobutyric acid, compared with mice that did not develop SE.

The level of propionyl-CoA, a metabolite of triheptanoin, declined in SE mice that were fed a standard diet. However, the triheptanoin diet increased levels of propionyl-CoA in SE mice.

Despite the fact that propionyl-CoA can be used to replenish levels of the citric acid cycle intermediate succinyl-CoA, the triheptanoin diet had no effect on the levels of citric acid cycle intermediates, including acetyl-CoA and succinyl-CoA. These effects indicated that the metabolism of triheptanoin is different in epileptic brain tissue, compared with normal brain tissue, which suggests that triheptanoin "may have more pronounced effects in 'diseased' compared to normal brain tissue," the authors wrote.

The research was funded by Citizens United for Research in Epilepsy and the National Institutes of Health. The investigators filed a provisional patent in the United States for their discovery.

*Research report by Managing Editor, Jeff Evans.*



Seizure development was delayed in mice fed a diet containing 35% triheptanoin (right) for 3 weeks, compared with mice fed a standard, sucrose-containing diet (left).

PHOTOS COURTESY KARIN BORGES, PH.D.

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cludes instances in which SUDEP cannot be ruled out either because there is a plausible competing explanation for death or there is insufficient information about the circumstances of death, he said.

Of the 26 patients, 15 were female and 11 were male, and all but 1 were taking at least one antiepileptic drug. Lamotrigine was the most frequently used drug (10 patients, including 9 women), followed by valproate (8), carbamazepine (7), vigabatrin (3), oxcarbazepine (3),

phenytoin (3), topiramate (2), and phenobarbital (1), Dr. Aurlen reported.

Based on these 26 cases, the investigators calculated the incidence of SUDEP to be 1 per 1,000 patient-years. But when only the definite and probable cases were included, the incidence was 0.7 per 1,000 patient-years, which is similar to the estimated incidence in Western countries, he said.

Of the 10 deaths in patients taking lamotrigine, 2 were classified as possible SUDEP and 8 as definite or probable SUDEP. The overall incidence of defi-

nite, probable, and possible SUDEP for patients treated with lamotrigine was 4.9 per 1,000 patient-years, compared with 0.7 per 1,000 patient-years for patients who were not treated with the drug. For definite and probable SUDEP, the incidence was 3.9 per 1,000 patient-years with lamotrigine vs. 0.46 per 1,000 patient-years with other antiepileptic drugs, Dr. Aurlen said.

In contrast, "the SUDEP incidence for carbamazepine, valproate, or the other drugs was not significantly different from the incidence among those

not treated with these."

Because 9 of the 10 victims on lamotrigine were females, Dr. Aurlen concluded their findings may suggest a gender difference. He and his associates are currently working with control group data "to see if there are factors other than lamotrigine that might explain the increased risk of SUDEP in this patient population."

None of the investigators had relevant financial disclosures.

*Mary Ann Moon contributed to this report.*

## ADVISER'S VIEWPOINT

# Will Triheptanoin Work?

The conventional mainstream approach to the treatment of epilepsy is to prescribe appropriate antiepileptic drugs. The vast majority of people with epilepsy use and rely upon AEDs to stop or at least reduce recurrent seizures to improve quality of life and reduce morbidity and mortality.

Unfortunately, a significant number of people with epilepsy do not adequately respond to AEDs, and thus require other therapies such as resective surgery, seizure devices, and the ketogenic diet. Surgery remains the current clinical standard in cases of medically refractory epilepsy in which a clear seizure focus can be identified and safely removed, offering a

chance for cure. The only device currently available for people with epilepsy in the United States is the vagus nerve stimulator, which is typically relegated for use in those who are not eligible or desirous of resective epilepsy surgery. Other devices for epilepsy that respond to or predict the tell-tale signs of a seizure are in various stages of development and evaluation. The ketogenic diet has been conventionally used to treat children, but also has been effectively employed in the adult epilepsy population. The use of the ketogenic diet was discovered essentially by serendipity decades ago, and over the years has been refined through clinical trials to maximize effectiveness.

Some people with epilepsy find that none of these conventional therapies is effective, which leads us to the very interesting article by Ms. Willis and her associates about using a diet rich in triheptanoin to reduce seizures in mice. The idea behind the experiment is that in

seizures, dysfunctional meta-

bolic processes in the brain deplete levels of citric acid cycle intermediates that help to create ATP in aerobic metabolism. This leads to increased neuronal hyperexcitability and reduced levels of the neurotransmitters glutamate, GABA, and aspartate, which are ultimately derived from these citric acid cycle intermediates. While the diet used in these experiments was found to have antiseizure properties, the exact mechanism of action remains elusive.

The nature of this discovery is not dissimilar to the way many compounds ultimately are discovered to have anti-seizure properties. Many of these compounds are found through drug discovery programs in

which the antiseizure property was noticed before the true mechanism of action was ultimately determined. The unique approach here is that the findings were realized beginning with a well-thought-out series of experiments using dietary manipulation. On the other hand, the diet used here may be analogous to the ketogenic diet, requiring years of refinement to optimize effectiveness and patient selection. It remains to be determined if a diet rich in triheptanoin translates into effective or even palatable therapy for people with epilepsy. The final story on this discovery may take years to write, but it is gratifying to those of us in the epilepsy community that researchers like Ms. Willis and her coauthors continue to work on the elusive cure for epilepsy.

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