# Ketogenic Diet May Help Some With Epilepsy

*Seizure control may improve with switch from the modified Atkins diet to the stricter ketogenic diet.*

BY DIANA MAHONEY

FROM THE ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY

SAN ANTONIO – Switching from the modified Atkins diet to the stricter ketogenic diet may improve seizure control in some patients with intractable epilepsy, a multinational, retrospective study has shown.

In particular, patients with myoclonic-astatic epilepsy, an idiopathic generalized epilepsy syndrome of early childhood, appeared to have the greatest likelihood of further improvement after making the switch, Dr. Eric Kossoff reported at the meeting.

Previous studies have suggested that children who have achieved seizure control with the stringent, high-fat, low-carbohydrate ketogenic diet can maintain that status when they transition to the less-restrictive modified Atkins diet; however, the possibility of achieving additional seizure control by switching from the modified Atkins to the ketogenic diet has not been investigated, said Dr. Kossoff of Johns Hopkins University, Baltimore.

The modified Atkins diet differs from the traditional Atkins program in its further restriction of carbohydrates and stronger encouragement of fat intake. Compared with the ketogenic diet, the modified Atkins diet does not restrict fluid, calories, or protein, and it relies on carbohydrate counts rather than food weight and measurement, Dr. Kossoff explained.

Dr. Kossoff and colleagues from Denmark, Germany, and South Korea found that 9 of 28 patients who made the change reduced the frequency of seizures by more than 10%; 5 of the 9 subsequently became seizure free.

The ketogenic diet did not improve seizures in another five children who previously had no improvement while on the modified Atkins diet.

The likelihood of improvement as a result of the dietary switch was 78% for patients with myoclonic-astatic epilepsy, which was significantly higher than the 11% reported for all other etiologies combined. All five children who became seizure free after transitioning to the ketogenic diet had myoclonic-astatic epilepsy.

"We also observed a trend toward greater likelihood of improvement if a child had fasted at the onset of the ketogenic diet, but this did not reach statistical significance," he said.

Further research into the mechanisms underlying the anticonvulsant effect of the diets is needed to determine when and in which patients to use them, Dr. Kossoff said.

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DR. KOSSOFF

Some insight into this question was provided at the meeting by Susan Masino, Ph.D., of Trinity College in Hartford, Conn., who presented the findings of a study that confirmed adenosine as a key factor in the anticonvulsant effect of the ketogenic diet.

Dr. Masino and her colleagues found that mice with normal levels of adenosine A1 receptor (A1R) and a transgenic overexpression of adenosine kinase, an intracellular enzyme that negatively influences extracellular levels of adenosine, had a "near complete" reduction in the number and duration of spontaneous seizures. But mice with reduced A1R levels and those that lacked A1Rs were partially or completely resistant to the diet therapy.

"When we injected glucose, which blocks A1Rs, into the mice with reduced seizures from the ketogenic diet, the seizure frequency returned to previous levels within 30-90 minutes," she said.

The ketogenic diet appears to reduce seizures by increasing A1R-mediated inhibition through its low carbohydrate nature, Dr. Masino said. The suggestion that ketogenic metabolism increases the activity of adenosine at the A1 receptor subtype "may offer insight into new therapies for epilepsy as well as other clinical conditions in which adenosine is known to have clinical benefits."

Dr. Kossoff has received consultant fees from Atkins Nutritionals Inc. Dr. Masino reported having no relevant financial disclosures. ■

# New Epilepsy Treatments Found Safe, Effective in Phase III

BY DIANA MAHONEY

FROM THE ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY

SAN ANTONIO – Treatment options for epilepsy may soon be expanding in light of the results of several recently reported phase III trials.

Two drugs, including one that has not yet been approved in any country, demonstrated efficacy and safety as adjunctive treatments for different forms of epilepsy.

Perampanel, a selective, noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist was tested as an add-on therapy for partial-onset seizures in the first of three multinational, placebo-controlled trials.

Adjunctive therapy with the benzodiazepine derivative clobazam significantly reduced the occurrence of drop seizures in the largest clinical trial to date in patients with Lennox-Gastaut syndrome.

## Perampanel

In the Eisai-sponsored study of perampanel, 712 patients aged between 12 and 72 years with refractory partial seizures were randomized to treatment with 2, 4, or 8 mg/day of perampanel or placebo following a 6-week baseline phase. The patients were being treated with one to three concomitant antiepileptic drugs, Dr. Gregory L. Krauss reported.

At the end of the 19-week treatment phase, the median change in seizure frequency from baseline for the intention-to-treat population was significant in the 4-mg and 8-mg groups, with reductions of 28.6% and 33.5%, respectively, compared with nonsignificant reductions of 16.3% and 13.8% in the 2-mg and placebo groups, respectively.

The treatment phase included 6-week titration and 13-week maintenance periods, according to Dr. Krauss, professor of neurology at Johns Hopkins University in Baltimore.

"The responder rates were similar," he noted, referring to the percentage of patients in each group who experienced at least a 50% reduction in seizure frequency during the maintenance phase relative to baseline. Nearly 29% of the 4-mg group and 35% of the 8-mg group were responders, compared with 21% of the 2-mg group and 17.6% of the placebo group, he said.

Treatment-related adverse events – most often dizziness, somnolence, and headache – caused a low number of patients in each group to withdraw from the trial. The few serious adverse events that occurred also were similarly distributed across the groups, according to Dr. Krauss.

In addition to confirming the safety and efficacy of 4 mg and 8 mg perampanel as an add-on treatment for partial-onset seizures, the findings also "help to establish the range of therapeutic doses and to identify the potential lower dose range for treatment," he said.

**Adjunctive therapy with 8 mg of perampanel decreased the mean frequency of seizures by 33.5%.**

DR. KRAUSS

## Clobazam

The frequency of drop seizures declined significantly for patients with Lennox-Gastaut Syndrome (LGS) who received the highest doses of clobazam in a double-blind, placebo-controlled trial.

"Patients in the 0.5-mg dose group experienced an average decrease of 47.8% and those in the 1.5-mg group had an average decrease of 69.5%," said Dr. Joan Conry of Children's National Medical Center in Washington.

Dr. Conry said that the drug "is much needed" because the drop attacks experienced by LGS patients often lead to injury.

In the trial, 238 patients aged 2-60 years with clinical and EEG-confirmed LGS who experienced drop seizures during a 4-week baseline phase were randomized to placebo or 0.25 mg, 0.5 mg, or 1.5 mg of clobazam up to a maximum daily dose of 40 mg. Following the treatment period (a 3-week titration phase and a 12-week maintenance phase), the investigators compared the percentage decrease in mean weekly drop seizures during the maintenance phase against the baseline rate for the modified intention-to-treat population of 217 patients.

Patients who experienced 75% and 50% reductions in drop seizures showed significant decreases relative to placebo in the medium- and low-dosage groups. Seizure frequency was reduced by 75% in 38% of patients who received 0.5 mg and 63% of patients who received 1.5 mg, compared with 11% of placebo-treated patients. Seizure reductions of at least 50% occurred in 59% of the medium-dosage group and 78% of the high-dosage group, compared with 32% of the placebo patients, she said.

The patients who were taking the high dosage of clobazam also had a significant decline in the frequency of nondrop seizures – a secondary study outcome – in comparison with placebo. Physician and caregiver global assessment scores also improved across all three of the dosages, Dr. Conry stated.

The most frequent adverse events observed included somnolence, lethargy, upper respiratory tract infections, drooling, and behavioral abnormalities, she noted.

Lundbeck, the manufacturer of clobazam and sponsor of the trial, will likely submit an application to the Food and Drug Administration in the first quarter of 2011, according to Dr. Conry. The drug is already available in more than 100 countries.

Dr. Krauss reported relationships with UCB Pharma, Bristol-Meyers Squibb, Eisai, SK Biosciences, and Johnson & Johnson. Dr. Conry received compensation from Lundbeck for the clobazam study. ■