Implant Short-Circuits Some Epileptic Seizures

BY DIANA MAHONEY

BOSTON — Patients with treatment-resistant epilepsy can reduce seizure frequency with the use of an implantable device that detects preseizure electrical activity and aborts seizures, the results of a multicenter, randomized trial suggest.

In 191 patients with medically intractable, partial onset seizures who were implanted with the neurostimulator, seizures declined by a mean of 29% during active stimulation with the device, compared with a 14% reduction during sham activation, Dr. Martha J. Morrell reported at the annual meeting of the American Epilepsy Society.

VITALS

Major Finding: Seizure frequency declined by a mean of 29% during active stimulation with the device over the first 12 weeks, compared with a 14% reduction during sham activation.

Data Source: Multicenter, randomized, sham-controlled clinical trial of 191 patients with medically intractable, partial onset seizures.

Disclosures: Dr. Morrell is the chief medical officer of NeuroPace, which developed the system and funded the trial.

In the later, open-label phase of the study in which all patients received active stimulation, nearly half of the 171 patients for whom 12 weeks of data were available had at least a 50% reduction in seizure frequency relative to baseline, said Dr. Morrell, clinical professor of neurology at Stanford (Calif.) University and chief medical officer of NeuroPace, developer of the Responsive Neurostimulator System (RNS).

The cranially implanted RNS device differs from conventional, "open loop" brain stimulation technologies that involve the scheduled delivery of electrical stimulation to specific brain regions independent of brain activity.

"The RNS delivers stimulation in response to a detected event," Dr. Morrell said. The "individualized and dynamic" treatment responds to patterns of brain activity specific to a patient's seizure pattern. The electrodes are implanted in epileptic regions of the brain and connected to the battery-powered neurostimulator embedded in the skull.

"The programming is done wirelessly by the physician via a laptop computer," Dr. Morrell said. "It's highly modifiable in that the physician can view the patient's electrocorticographic activity in real-time and change the [signal-detection] criteria at any time based on individual patient characteristics."

Up to two leads, each containing four electrodes, can be connected to the neurostimulator, so the system can monitor and stimulate two distinct epileptogenic zones independently, she noted.

Because the neurostimulation occurs in response to aberrant electrical activity, fewer electrical impulses are delivered than would occur with continuous stimulation. This diminishes the risk of treatment-related adverse events, Dr. Morrell explained.

In an initial feasibility study of 65 patients, the responsive neurostimulation system demonstrated excellent safety, tolerability, and preliminary evidence of efficacy, Dr. Morrell said. "There were no serious device-related adverse events, and stimulation-related symptoms experienced by several subjects were addressed by adjusting the stimulation settings."

A minimum 50% reduction in seizure frequency was achieved in 43% of the patients with complex partial seizures and 35% of those with total disabling seizures (Neurotherapeutics 2008;5:68-74).

In the double-blind pivotal trial, the 191 patients were randomized to active or sham therapy. All were 18-70 years of age (median 35 years), and all had partial onset epilepsy localized to one or two foci and had failed at least two antiepileptic medications.

The patients were taking an average of three antiepileptic medications to attempt seizure control; 34% had been treated previously with vagus nerve stimulation, 33% had prior surgical resection, and 16% had been treated with both.

"These patients tended to be very ill. Most of them had epilepsy for more than 20 years, and many were having at least three seizures per 28-day period—often many more than that," Dr. Morrell said.

Of the 191 patients implanted with the device, 50% had mesial temporal seizure onset, 42% had neocortical seizure onset, and 8% had both, Dr. Morrell said at a press briefing during the meeting.

An initial, 12-week period prior to system implantation, during which baseline seizure activity was collected, was followed by a 12-week blinded period when participants were randomly assigned to have the responsive stimulation activated or left inactive, she said.

At each of the 31 trial sites, the patients and one neurologist were blinded to stimulation status, while a separate neurologist programmed the devices in order to maintain the study blinding. The responsive stimulation was optimized in the treatment over the next 4 weeks, followed by 84 days of data collection. At the end of the blinded efficacy period, stimulation was activated for all of the study participants for 2 years.

There were no serious, unanticipated device-related adverse events during the trial, nor was there a difference between the two groups with respect to the rate of adverse events, including depression, memory impairment, and anxiety, Dr. Morrell reported.

The findings suggest that responsive neurostimulation might be a promising treatment option for patients with seizures that are resistant to conventional antiepileptic therapy. The apparent increase in the number of patients experiencing at least a 50% reduction in seizure frequency relative to baseline during the open-label phase of the study suggests the system might become more effective over time, she noted.

The system has not yet received Food and Drug Administration approval, but NeuroPace plans to submit a premarket approval application to the FDA in early 2010, Dr. Morrell said. ■

Anticonvulsant Drugs Linked to Reduced Bone Mineral Density

BANGKOK, THAILAND — Long-term antiepileptic drug therapy is associated with poorer bone health in premenopausal women.

Dr. Rungsan Chaisewikul of Siriraj Hospital, Bangkok, included 50 women with epilepsy and 51 matched controls in his study, presented during the meeting's poster session. All of the women were premenopausal, with a mean age of 33 years. Patients had been on antiepileptic drugs (AEDs) for at least 3 years. Most of the women (62%) were taking more than one drug, and most (84%) were taking an enzyme-inducing AED. All participants had bone mineral density (BMD) measured at the lumbar spine, left femur, and left radius.

Compared with the controls, the patients had significantly lower T scores at the femoral neck (0.30 vs. –0.08). BMD at the lumbar spine was lower, but not significantly lower, in patients than in controls, as was BMD at the radius.

Based on measurements at the femoral neck and lumbar spine, significantly more patients than controls were rated as having osteopenia and osteoporosis. More patients than controls also were rated as osteopenic or osteoporotic when considering the radius measurement, although that difference was not statistically significant.

—Michele G. Sullivan

In Utero Valproate May Impair Language

BY MICHELE G. SULLIVAN

BANGKOK, THAILAND — Expressive and receptive language abilities are lower in 3-year-olds who were exposed to sodium valproate in utero than in children exposed to other individual antiepileptic drugs during gestation, according to a subanalysis of the Neurodevelopmental Effects of Antiepileptic Drugs study.

Valproate exposure was associated with a 10-point difference on both language measures compared with exposure to phenytoin, carbamazepine, or lamotrigine—a difference that is statistically significant and clinically important, Gus A. Baker, Ph.D., said at the World Congress of Neurology.

The prospective, observational Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study included 303 pregnant women taking sodium valproate, carbamazepine, lamotrigine, or phenytoin as monotherapy. Enrollment occurred during 1999-2004 in 25 epilepsy centers in the United States and the United Kingdom. The primary outcome is cognitive performance of the children at 6 years of age.

Dr. Baker, a primary investigator in the U.K. study and coinvestigator in the overall study, presented the results of the drugs' effect on expressive and receptive language development among 234 children who were 3 years old at the time of assessment. Test scores were adjusted for factors known to affect child intellect, including maternal IQ, maternal age, gestational age, antiepileptic drug (AED) dose, and prenatal exposure to folate.

"Maternal IQ, AED dose, maternal age, gestational age, and preconceptional exposure to folate were significant factors predicting the scores, as we would expect," said Dr. Baker, director of the division of neurosciences at the Walton Centre for Neurology and Neurosurgery, Liverpool, England, and professor of clinical neuropsychology at the University of Liverpool. "But we also showed that overall, the scores for valproate-exposed children were significantly lower than all other drugs and the magnitude of the effect was greater for verbal than nonverbal language."

Testing showed that the children exposed to valproate scored significantly lower on measures of expressive language (mean score of 91 vs. 102 for carbamazepine, 104 for lamotrigine, and 101 for phenytoin) and receptive language (mean score of 89 vs. 97 for carbamazepine, 101 for lamotrigine, and 101 for phenytoin). On visual motor construction and nonverbal intellectual ability, children exposed to valproate scored lower, but not significantly lower, than children exposed to the other drugs.

The study confirms earlier NEAD findings, which strongly suggest that women of childbearing age who need AED therapy should avoid valproate if possible. "For women for whom sodium valproate is the first choice because of the nature of their seizures, we should be thinking about reducing the dose to the least possible effective level," Dr. Baker said. "In an ideal world, we would have preconception counseling and would be thinking of an alternative drug several years before pregnancy occurs." ■