DBS: An Evolving Tx for Refractory Epilepsy

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MADRID — Deep brain stimulation shows considerable promise for reducing intractable seizures in patients who are not candidates for epilepsy surgery, even though there have been few large-scale controlled trials to back up the practice.

"We have no idea what the best stimulation parameters are, we don't know whether to stimulate in response to epileptiform activity or continuously, and, of course, the search for the optimal target is ongoing," Dr. Paul Boon said at the annual congress of the European Federation of Neurological Societies.

"Most of our information has come from uncontrolled studies and case reports, which included about 115 people worldwide."

Now, data from three new or upcoming studies might help shed light on some of these questions, said Dr. Boon of University Hospital Ghent (Belgium), where he and his colleagues are leaders in researching an epilepsy application for DBS.

Some of the earliest studies, in the 1980s and early 1990s, used the electrodes in the brain's cerebellar regions, but with very little effect, so the cerebellum is no longer considered a target. The caudate nucleus and centromedial nucleus of the thalamus have also been examined as possible targets, but in very small numbers of patients and with varying results, said Dr. Boon.

The most promising approach to date is bilateral stimulation of the anterior thalamic nucleus, he said. Early uncontrolled studies of this application had small patient numbers, but their success led to the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial of 110 patients with medically refractory partial-onset seizures.

All of the patients received the implants; for the first 3 months, only half of the patient had their stimulators turned on. After this blinded treatment phase, all of the patients received neurostimulation. By way of detailing his financial conflicts of interest, Dr. Boon said in an interview that Medtronic Inc., the company that makes DBS hardware, has been and is providing devices and electrodes in support of the pilot trial, and has provided an educational grant.

The medial temporal lobe and the hippocampus are other potential targets. Last year, Dr. Boon and his colleagues published a study of 12 patients with refractory temporal lobe epilepsy, who were also candidates for surgery. Instead of implanting recording electrodes during the presurgical period, they implanted DBS electrodes in the medial temporal lobe.

"We aimed to adjust the simulation parameters to get a 50% reduction in spikes for 7 consecutive days," he said. "If the patient achieved that, then we went to chronic stimulation, and if they did not achieve that, then we adjusted the parameters until we met those criteria. If the patient still didn't achieve the reduction, then we removed the electrodes and proceeded to surgery."

Of the 12 patients, 10 underwent long-term DBS and 2 had the resection. After a mean follow-up of 31 months, both of the surgical patients were seizure free. One of the DBS patients had a seizure reduction of more than 90%; five had a reduction of at least 50%, and two had a reduction of 30%-40% (Epilepsia 2007;48:1551-60).

"We got a 70% response rate, with no significant adverse events or changes in memory," he said. "This shows that DBS of the medial temporal lobe is safe, feasible, and effective."

Dr. Boon and his group are also seeking to recruit 45 patients for a study comparing DBS of the hippocampus with medial temporal lobe resection or with hippocampal DBS delayed for 6 months after implantation. The 1-year trial will also be sponsored by Medtronic.

Researchers believe that DBS controls seizures by desynchronizing synchronized high-voltage cortical discharges. During chronic DBS, the stimulation is applied constantly to the epileptogenic focus, regardless of the area's own discharge.

However, there is some evidence that stimulation only in response to epileptiform activity might be more effective. This "closed-loop" stimulation would require a device that could read and analyze brain waves and then "decide" what type of stimulation to deliver.

Early external devices were tested in small numbers of patients in the late 1990s and early 2000s. More recently, a California-based company, NeuroPace Inc., has developed the RNS System, which includes fully implantable intracranial components as well as external products, Dr. Boon said.

The device consists of an implanted neurostimulator with one or two strip leads that can be placed in different areas of the brain to allow activity to be monitored and controlled.

An external programming device allows the stimulator to detect predetermined electrographic patterns; the physician can also program the type of response that the device delivers. ■

Antiepileptic Age, Polytherapy Linked to More Adverse Effects

MADRID — Adverse events are more common in patients who take older antiepileptic drugs or who take more than one antiepileptic, compared with those on monotherapy or newer agents.

"The adverse effect profiles of antiepileptic drugs are often determining factors in drug selection, and yet adverse effects may be overlooked in everyday clinical practice," Joyce A. Cramer wrote in a poster presented at the annual congress of the European Federation of Neurological Societies.

Ms. Cramer, a research scientist at Yale University, New Haven, Conn., conducted a population surveillance study in six European countries to evaluate the adverse effects of both newer and older antiepileptic drugs (AEDs).

The study population comprised 1,019 patients (mean age, 31 years) who had been on a stable dosing regimen for a median of 13 months. Of those, 57% were on monotherapy, and 43% were on polytherapy. Most of the patients (71%) were taking at least one older AED (carbamazepine, clobazam, clonazepam, phenobarbital, phenytoin, or valproate). The rest were taking at least one newer AED (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide).

At least one adverse effect occurred in 68% of the patients. Newer AEDs were associated with fewer reports of adverse effects than were older drugs (61% vs. 71%, respectively), and monotherapy was associated with fewer reports of adverse effects than was polytherapy (66% vs. 71%).

Neurologic adverse effects were more common in those taking older AEDs than in those taking newer AEDs (60% vs. 54%, respectively), as were systemic adverse effects (42% vs. 33%).

Neurologic adverse effects were also more common in patients on polytherapy than in those on monotherapy (64% vs. 53%), although the percentage of patients reporting systemic adverse effects was equal in these two groups (40%).

Adverse effects that were significantly more common in those taking the older drugs, compared with newer ones, were cognitive slowing (30% vs. 22%), sedation (30% vs. 23%), and tremor (18% vs. 10%).

Adverse effects that were significantly more common in those taking polytherapy, compared with monotherapy, were cognitive slowing (36% vs. 22%), psychological problems (31% vs. 22%), tremor (21% vs. 11%), and gait disturbances (12% vs. 7%).

A logistic regression analysis concluded that patients on newer AEDs were 36% less likely than were those on the older drugs to report at least one adverse effect. Treatment modifications were 52% more likely in those reporting adverse effects.

The study was sponsored by UCB Pharma Inc., which makes levetiracetam. Ms. Cramer is a consultant for the company. ■

Lacosamide Brings Control to Treatment-Resistant Epilepsy

MADRID — The investigational antiepileptic lacosamide is well tolerated and reduced seizures by more than 50% in almost half of patients who took it as adjunctive therapy for medication-refractory partial seizures.

"This study, with more than 5 years of follow-up, showed that lacosamide controls these seizures very well," Dr. William Rosenfeld said at the annual congress of the European Federation of Neurological Societies.

Lacosamide is also being investigated for neuropathic pain, said Dr. Rosenfeld, medical director of the Comprehensive Epilepsy Care Center for Children and Adults in St. Louis. The drugmaker, UCB Inc. of Brussels, received a not approvable letter from the Food and Drug Administration for this indication in late July, although the agency is still considering the drug's use as an add-on therapy for partial-onset seizures.

The phase III trial was an open-label extension study that comprised 370 adults (mean age 40 years) who had previously participated in placebo-controlled studies of the drug. The mean follow-up time was 5.5 years. At baseline, all patients had partial seizures that remained uncontrolled despite numerous medication trials; more than half of the cohort had tried seven or more drugs during their lifetime.

Study protocol allowed titration of up to 800 mg/day; lacosamide could be used as either add-on therapy or monotherapy at the clinicians' discretion. The most commonly used dosage was 400 mg/day (24%).

Overall, 46% of patients taking the drug experienced a reduction in seizures of at least 50%. This response rate was apparent by 6 months and continued to improve, with 65% responding by 30 months.

"This doesn't mean, however, that the drug was getting more effective as time went on," Dr. Rosenfeld said. "It's a function of adjusting the dose and having nonresponders drop out."

Adverse events were dizziness (37%), which was transient and usually ceased as patients adjusted to the medication; headache (18%), fatigue, and nasopharyngitis (14% each); and diplopia, abnormal vision, and upper respiratory tract infection (13% each). There were no significant cognitive side effects, Dr. Rosenfeld said.

According to the company Web site, lacosamide has a novel dual method of action, selectively enhancing slow inactivation of voltage-gated sodium channels, and modulating collapsin response mediator protein 2 (CRMP-2).

Dr. Rosenfeld has been a principal investigator in several of the company-sponsored lacosamide studies. ■