

DEEP BRAIN STIMULATION FOR INTRACTABLE EPILEPSY: WHICH TARGET AND FOR WHICH SEIZURES?

Electrical Stimulation of the Anterior Nucleus of the Thalamus for the Treatment of Intractable Epilepsy

Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N

Epilepsia 2004;45(4):346–354

PURPOSE: Animal studies and sporadic case reports in human subjects have suggested that intermittent electrical stimulation of the anterior nucleus of the thalamus reduces seizure activity. We embarked on an open-label pilot study to determine initial safety and tolerability of bilateral stimulation of the anterior nucleus of the thalamus (ANT), to determine a range of appropriate stimulation parameters, and to begin to gather pilot efficacy data.

METHODS: We report an open-label pilot study of intermittent electrical stimulation of the ANT in five patients (three men, two women; age range, 24–47 years), with follow-up between 6 and 36 months. All patients had intractable partial epilepsy. Four of the five patients also had secondarily generalized seizures. Stimulation was delivered by bilateral implantable, programmable devices by using an intermittent, relatively high-frequency protocol. Stimulation parameters were 100 cycles per second with charge-balanced alternating current; pulse width, 90 msec; and voltages ranging between 1.0 and 10.0 V. Seizure counts were monitored and compared with preimplantation baseline.

RESULTS: Four of the five patients showed clinically and statistically significant improvement with respect to the severity of their seizures, specifically with respect to the frequency of secondarily generalized tonic-clonic seizures and complex partial seizures associated with falls. One patient showed a statistically significant reduction in total seizure frequency. No adverse events could clearly be attributed to stimulation. None of the patients could determine whether the stimulator was on or off at these parameters.

CONCLUSIONS: Electrical stimulation of the ANT appears to be well tolerated. Preliminary evidence suggests clinical improvement in seizure control in this small group of intractable patients. Further controlled study of deep brain stimulation of the anterior nucleus is warranted.

COMMENTARY

Deep brain stimulation has gained a significant therapeutic role in the treatment of various neurologic disorders, including movement disorders, chronic pain, and epilepsy. In epilepsy, deep brain stimulation is used to target various neuroanatomic structures, such as the anterior and centromedian nuclei of the thalamus, the subthalamic nucleus, the cerebellum, and more recently, the hippocampal formation.

High-frequency electrical stimulation of the anterior nucleus of the thalamus (ANT) and of brain structures that project to the ANT was shown to reduce or inhibit seizure activity in animal models of epilepsy (1,2). Although it is suspected that lesioning of the ANT plays a role in the suppression of seizure activity, a more likely mechanism is the desynchronization of high-voltage synchronized cortical discharges, which renders the cortex less susceptible to seizures (2,3).

The first report of a promising therapeutic effect of deep brain stimulation of the ANT was published in 1987 by Upton and Cooper (4), who found a reduction in seizure frequency in four of six patients. In the present study, Kerrigan et al. present the results of an open-label pilot study of intermittent electrical stimulation of the ANT in five patients with refractory epilepsy. The impact of deep brain stimulation of the ANT in the overall seizure frequency was not impressive at all, as no significant decrease was seen in the total number of seizures after 12 months. A significant reduction in seizure frequency was observed when the analysis was restricted to generalized tonic-clonic seizures or partial seizures. Another open-label study of five patients yielded a better therapeutic response, with a mean reduction of 54% in seizure frequency and with two patients experiencing a 75% decrease in the number of seizures (5). Clearly, no definite conclusions can be derived from small open-label studies of five or six patients, and judgment must be reserved until data from a

large multicenter, prospective, randomized, placebo-controlled study are completed. Such a study is now under way in the United States.

High-frequency stimulation of the centromedian thalamic nucleus also results in desynchronization of cortical EEG activity in both animal models (6) and human studies (7,8) of epilepsy. The first study of electrical stimulation of this structure in humans was conducted by Velasco et al. in Mexico, involving 23 patients with secondarily generalized epilepsy or mixed seizure disorders (7). After 3 months of stimulation, an 80% to 100% reduction was found in generalized tonic-clonic seizures and a 60% to 100% decrease in atypical absence seizures. Complex partial seizures were not affected by the electrical stimulation. After a 5-year follow-up period, a benefit was seen in 50% of patients. In a double-blind pilot study using a crossover design [3 months of centromedian thalamic nucleus stimulation or placebo, 3 months "washout" (i.e., no stimulation), and 3 months of treatment opposite to the patient's first 3-month treatment], Fisher et al. demonstrated a therapeutic effect but of much lesser magnitude than found in the Velasco et al. study. Only a 30% reduction was seen in the frequency of generalized tonic-clonic seizures during stimulation compared with 8% during the washout period (8).

The subthalamic nucleus also has been the target of deep brain stimulation in experimental and human studies (9–11). A first open-label study in humans included four patients who underwent high-frequency subthalamic nucleus stimulation, yielding a more than 50% reduction in seizure frequency in all patients (10). In a second open-label study of four patients by a different group of investigators, subthalamic nucleus stimulation yielded a more than 50% reduction in seizure frequency in only one patient (11). Clearly, the limited data from these two small studies are less than encouraging.

To date, the efficacy of deep brain stimulation in the management of intractable epilepsy is not yet established. Large double-blind, placebo-controlled studies that compare the efficacy of deep brain stimulation among the ANT, centromedian thalamic nucleus, and subthalamic nucleus must be carried out to establish the ideal neuroanatomic target(s). Data, so far, seem

to suggest that generalized tonic-clonic seizures are probably more likely to be affected by deep brain stimulation than are other seizure types, but this question also must be answered in controlled studies.

by *Andres M. Kanner, M.D.*

References

1. Mirski MA, Rossell LA, Terry JB, Fisher RS. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. *Epilepsy Res* 1997;28:89–100.
2. Mirski MA, Ferrendelli JA. Anterior thalamic mediation of generalized pentylentetrazol seizures. *Brain Res* 1986;399:212–223.
3. Hamani C, Ewerton FI, Bonilha SM, Ballester G, Mello LE, Lozano AM. Bilateral thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. *Neurosurgery* 2004;54:191–195.
4. Upton ARM, Amin I, Garnett S, et al. Evoked metabolic responses in the limbicstriate system produced by stimulation of the anterior thalamic nucleus in man. *Pacing Clin Electrophysiol* 1987;10:217–225.
5. Hodaie M, Wennberg RA, Dostrovsky JO, et al. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia* 2002;43:603–608.
6. Miller JW, Ferrendelli JA. The central medial nucleus: thalamic site of seizure regulation. *Brain Res* 1990;508:297–300.
7. Velasco F, Velasco M, Velasco ML, et al. Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long term studies. *Epilepsia* 1995;36:63–71.
8. Fisher RS, Uematsu S, Kraus GL, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in the treatment of intractable seizures. *Epilepsia* 1992;33:841–851.
9. Dybdal D, Gale K. Postural and anticonvulsant effects of inhibition of the rat subthalamic nucleus. *J Neurosci* 2000;20:6728–6733.
10. Benabid AL, Minotti L, Koudsie A, deSaint Martin A, Hirsch E. Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luyisi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up. *Neurosurgery* 2002;50:1385–1391.
11. Neme S, Luders H. Estimulacion cerebral profunda en Epilepsia. In: Campos MG, Kanner AM, eds. *Epilepsias: diagnostico y tratamiento*. Santiago, Chile: Editorial Mediterraneo, 2004:680–688.