References

1. Elble RJ. The pathophysiology of tremor. In: Watts RL, Koller WC, editors. Movement disorders: neurologic principles and practice. New York: McGraw-Hill; 1997. p 405–417.
2. Yang YW, Chang FC, Tsai CH, et al. Clinical and magnetic resonance imaging manifestations of Holmes tremor. Acta Neurol Taiwan 2005;14:9–15.
3. Remy P, de Recondo A, Defer G, et al. Peduncular "rubral" tremor and dopaminergic denervation: a PET study. Neurology 1995;45: 472–477.
4. Camps M, Cortes R, Gueye B, Probst A, Palacios JM. Dopamine receptors in human brain: autoradiographic distribution of D2 sites. Neuroscience 1989;28:275–290.
5. Brooks DJ. Dopamine agonists: their role in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 2000;68:685–689.
6. Baas HK, Schueler P. Efficacy of cabergoline in long-term use: results of three observational studies in 1,500 patients with Parkinson's disease. Eur Neurol 2001;46(Suppl. 1):18–23.
7. Inzelberg R, Nisipeanu P, Rabey JM, et al. Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. Neurology 1996;47:785–788.

An Open-Label Trial of Levetiracetam for Treatment of Cervical Dystonia

Levetiracetam is a novel antiepileptic drug approved for treatment of partial seizures. Its mechanism of action is uncertain. It does not interact with inhibitory or excitatory brain neurotransmitters. It appears to prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity and has been effective in suppressing paroxysmal dystonia in a hamster model[1] and levodopa dyskinesia in MPTP-lesioned marmoset monkeys.[2] In clinical reports, levetiracetam improved myoclonus,[3,4] L-dopa dyskinesia,[5] tardive dyskinesia,[6] and paroxysmal kinesiogenic choreoathetosis,[7] although essential tremor was unaffected.[8] The dose range used in these studies was 500 to 3,000 mg/day. One patient with blepharospasm, oromandibular dystonia, and mild cervical dystonia was successfully treated with levetiracetam, 1,500 mg/day, suggesting that it might also be helpful in the treatment of dystonia.[9] We carried out an open-label pilot study of levetiracetam in the treatment of cervical dystonia.

The protocol was approved by the Institutional Review Board, and informed consent was obtained from all patients. Ten patients with primary idiopathic cervical dystonia (CD) attending our dystonia botulinum toxin outpatient clinic were recruited for participation in an open-label clinical trial of levetiracetam. Patients were offered participation in the trial regardless of their response to botulinum toxin. Patients with primary and stable CD with duration of at least 3 years were eligible. Patients with secondary forms of torticollis, epilepsy, active psychiatric disorder, treatment with other anticonvulsant medications, previous sensitivity to levetiracetam, and pregnancy were excluded. There were 5 women and 5 men. Mean age was 54.1 ± 12.4 years; mean duration of CD was 9.6 ± 7.4 years. Four patients had rotational torticollis, 2 had laterocollis, 1 had retrocollis, and 3 had a mixed pattern. Five patients had dystonic head tremor. Responses to botulinum toxin were excellent in 5 patients and moderate in 5 patients. Two patients had developed immune-mediated resistance to Botox and Myobloc and were no longer receiving botulinum toxin. Patients were enrolled into a 7-week, open-label trial that began at least 14 weeks after the last administration of botulinum toxin. Patients were examined at weeks 0, 1, 3, 5, and 7 weeks, with telephone contact at weeks 2 and 4. After an initial baseline visit (week 0), levetiracetam 250 mg b.i.d. was initiated at week 1. Dose was increased to 500 mg b.i.d. at week 2 and 1,000 mg b.i.d. at week 3. Dose was maintained at 1,000 mg b.i.d. until the medication was discontinued at week 5. A post-treatment evaluation was carried out at week 7. Inquiry was made regarding adverse effects at each contact. Depending on severity, if adverse effects were reported, the dose was either kept unchanged or reduced to the previous level. Severity of CD was assessed with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) at each visit,[10] and a standardized video recording was recorded at baseline and week 5. The primary outcome measure was change in the TWSTRS scores from baseline to final visit on medication (week 5). Secondary outcomes were improvement in CD as determined by review of the video recordings and the patient's global impression of change.

Five of the 10 patients completed the trial. Four reached 1,000 mg b.i.d., and 1 reached 250 mg b.i.d. Two dropout patients reached 1,000 mg b.i.d. One dropped out at week 5 due to vomiting; the other dropped out at week 5 due to lack of improvement. One patient dropped out at week 2 on 250 mg b.i.d. due to drowsiness, and one dropped out at week 3 on 500 mg b.i.d. due to drowsiness and myalgias. All dropout patients were assessed at the time of study termination and last observation carried forward (LOCF) was used for analysis. One patient dropped out at visit 1 before beginning treatment and is not included in the analysis. TWSTRS scores at baseline and final visit were compared in the 5 patients who completed the trial and the 2 patients who dropped out at week 5 but reached the target dose of 1,000 mg b.i.d. with LOCF. There was no significant change in TWSTRS total score (37.4 ± 9.6 vs. 35.7 ± 11.1); TWSTRS severity subscore (16.7 ± 6.1 vs. 17.0 ± 6.5); TWSTRS disability subscore (11.0 ± 4.5 vs. 11.3 ± 6.0); or TWSTRS pain subscore (9.7 ± 2.3 vs. 8.3 ± 3.1). No patient reported subjective improvement in symptoms of CD. There was also no improvement in dystonic head tremor in the 5 patients with this manifestation. Comparison of video recordings and patient global impression of change before and after treatment also showed no change. Adverse effects were drowsiness with fatigue in 8 patients; gastrointestinal symptoms in 4 patients (vomiting, heartburn, abdominal cramps, tongue burning); dizziness, headache, and increased neck pain in 3 patients each; central nervous system symptoms in 3 patients (depersonalization, insomnia, impaired concentration); upper respiratory symptoms in 3 patients; and paresthesias, myalgias, hypotension, and urinary frequency in 1 patient each.

Although preclinical studies and case reports have suggested that levetiracetam may be helpful in the treatment of several dyskinetic and dystonic movement disorders,[5–7] this open-label trial found no improvement in CD and a high drop-out rate. Similar to previous clinical trials with levetiracetam,[5,8] drowsiness with fatigue was the most common troublesome adverse effect in this group of patients. No patient reported improve-

Published online 28 March 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.20873

ment in symptoms of CD or elected to continue treatment after conclusion of the study.

Acknowledgments: This research was supported by UCB Pharma and the Grand Circle Foundation. We thank Linda Paul, NP, and Lisa Scollins, NP for their assistance.

Daniel Tarsy, MD*
R. Kevin Ryan, MD
Susie I. Ro, MD
Department of Neurology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts
**E-mail: dtarsy@bidmc.harvard.edu*

References

1. Loscher W, Richter A. Piracetam and levetiracetam, two pyrrolidone derivatives, exert antidystonic activity in a hamster model of paroxysmal dystonia. Eur J Pharmacol 2000;391:251–254.
2. Hill MP, Bezard E, McGuire SG, et al. Novel antiepileptic drug levetiracetam decreases dyskinesia elicited by L-Dopa and ropinirole in the MPTP-lesioned marmoset. Mov Disord 2003;18:1301–1305.
3. Krauss GL, Bergin A, Kramer RE, Cho YW, Reich SG. Suppression of posthypoxic and postencephalitic myoclonus with levetiracetam. Neurology 2001;56:411–412.
4. Schauer R, Singer M, Saltuari L, Kofler M. Suppression of cortical myoclonus by levetiracetam. Mov Disord 2002;17:411–415.
5. Zesiewicz TA, Sullivan KL, Maldonado JL, Tatum WO, Hauser RA. Open-label pilot study of levetiracetam (Keppra) for the treatment of levodopa-induced dyskinesias in Parkinson's disease. Mov Disord 2005;20:1205–1209.
6. McGavin CL, John V, Musser WS. Levetiracetam as a treatment for tardive dyskinesia: a case report. Neurology 2003;61:419–420.
7. Chatterjee A, Louis ED, Frucht S. Levetiracetam in the treatment of paroxysmal kinesiogenic choreoathetosis. Mov Disord 2002;17:614–615.
8. Handforth A, Martin FC. Pilot efficacy and tolerability: a randomized, placebo-controlled trial of levetiracetam for essential tremor. Mov Disord 2004;19:1215–1221.
9. Zesiewicz TA, Louis ED, Sullivan KL, Menkin M, Dunne PB, Hauser RA. Substantial improvement in a Meige's syndrome patient with levetiracetam treatment. Mov Disord 2004;19:1518–1521.
10. Tarsy D. Comparison of clinical rating scales in treatment of cervical dystonia with botulinum toxin. Mov Disord 1997;12:100–102.