Levetiracetam for Phasic Spasticity in Multiple Sclerosis

Kathleen Hawker, MD; Elliot Frohman, MD, PhD; Michael Racke, MD

Background: Spasticity is a common and debilitating symptom of multiple sclerosis (MS). Current treatments are effective, but may be difficult to tolerate for many patients.

Objective: To determine if levetiracetam, a second-generation antiepileptic drug, may be useful for the treatment of spasticity in MS.

Methods: A retrospective medical record review of patients attending the Multiple Sclerosis Program at the University of Texas, Southwestern Medical Center at Dallas was performed. A series of 12 patients who had been treated with levetiracetam for spasticity was identified. Most of the patients were female (10/11), and the mean age was 41.0 years. The main outcome measure was a change in Penn spasm score or modified Ashworth score. Both scores are measured on a scale of 0 to 4.

Results: The Penn Spasm score (a measure of phasic spasticity) was decreased for all patients following treatment with levetiracetam. The mean±SD Penn Spasm score was 2.7±0.65 at baseline and decreased to 0.9±0.29 at follow-up. There was no change in modified Ashworth scores (a measure of tonic spasticity). Five patients reported adverse events; 1 patient discontinued treatment owing to an adverse event (edema). Three patients incidentally reported improvements in neuropathic pain.

Conclusions: Levetiracetam was effective for reducing phasic spasticity but not tonic spasticity in this 12-patient case series. The drug was well tolerated and therefore shows promise as a treatment for phasic spasticity. Large, well-controlled trials are needed to confirm these findings.

Arch Neurol. 2003;60:1772-1774

S

PASTICITY (a velocity-dependent increase in muscle tone) is a common symptom in multiple sclerosis (MS) due to demyelinating lesions in the spinal cord and brainstem. Spasticity produces stiffness and fatigability of the muscles as well as spasms, painful cramps, and clonus. Although rigorous studies on the mechanism of action have not been done, clinically, spasticity seems to be composed of 2 types: phasic spasticity, which begins with spasms, painful cramps, and clonus, and tonic spasticity, which produces stiffness. Spasticity may limit ambulation, impair balance, increase the risk of falls, produce pain, increase exertional fatigue, and interrupt sleep.

Historically, baclofen, dantrolene, benzodiazepines, and tizanidine have been used to treat painful spasms. Although proven efficacious, these medications are associated with a high incidence of sedation or weakness and may produce untoward effects on cognition and balance in patients with MS. Hepatotoxicity is also a well-recognized complication of dantrolene, and abnormal liver test results have been reported with both tizanidine and baclofen therapy.

Recent studies have indicated that an antiepileptic drug, gabapentin, may be effective in treating spasticity. In our clinical experience, the drug seems to have greater efficacy for cramps and spasms (phasic spasticity) than for the stiffness associated with spasticity (tonic spasticity), although an effect on both types of spasticity has been noted in the published literature. The precise mechanism responsible for the effectiveness of gabapentin is not known.

We hypothesized that other second-generation antiepileptics may also benefit patients with spasticity. Levetiracetam is a second-generation antiepileptic drug approved in 1999 as adjunctive treatment for partial-onset epilepsy. Its mechanism of action has not been fully elucidated, but it is known to promote inhibitory neurotransmission via indirect modulation of γ-aminobutyric acid, and glycine receptors and...
to depress high-voltage–activated calcium currents by inhibiting N-type calcium channels. Although, based on a MEDLINE search, no data have been reported on the use of levetiracetam for spasticity, it has shown preliminary efficacy in the treatment of neuropathic pain in humans and in an animal model of neuropathy. Clinical studies in epilepsy have demonstrated that levetiracetam is well tolerated, with a generally benign adverse-effect profile. Somnolence was the most frequently reported adverse event. Cognitive adverse effects (defined as terms coded as amnesia, confusion, and abnormal thinking in COSTART) were rarely reported in clinical trials (1%-1.6% for levetiracetam vs 0.3%-1.4% for placebo). Significant improvements in cognition (as compared with placebo) were self-reported by epilepsy patients who participated in a quality of life study. The pharmacokinetic profile of levetiracetam is uncomplicated: it demonstrates linear kinetics, has no appreciable protein binding (<10%), and is not known to interact with any drugs. The drug is eliminated renally, with a generally benign adverse-effect profile. Somnolence was the most frequently reported adverse event. Cognitive adverse effects (defined as terms coded as amnesia, confusion, and abnormal thinking in COSTART) were rarely reported in clinical trials (1%-1.6% for levetiracetam vs 0.3%-1.4% for placebo). Significant improvements in cognition (as compared with placebo) were self-reported by epilepsy patients who participated in a quality of life study.

Given the high incidence of underlying cognitive problems in patients with MS (45%-65%) and the need for polypharmacy to adequately treat MS, we felt that levetiracetam might offer unique safety benefits in this population. Also, we had used it to treat patients with spasticity in our clinic. We then performed a retrospective medical record review to assess its usefulness more systematically.

### METHODS

Data were abstracted from the medical records of all patients from the Multiple Sclerosis Program at the University of Texas, Southwestern Medical Center at Dallas, who had been treated with levetiracetam for MS-associated spasticity between January 2001 and June 2002. A total of 11 patient records were selected. The primary efficacy end point was change in Penn Spasm score (a measure of phasic spasticity) from baseline to follow-up. A secondary efficacy end point was change in modified Ashworth score (a measure of tonic spasticity) from baseline to follow-up. Both end points are measured on a scale of 0 to 4; a score of 0 reflects no spasms (Penn scale) or normal tone (Ashworth scale) while a score of 4 reflects at least 10 spasms per hour (Penn scale) or rigidity of the affected part(s) during flexion or extension (Ashworth scale). Demographics, dose, duration of treatment, and adverse events were also collected.

### RESULTS

We reviewed a total of 11 medical records of patients diagnosed as having spasticity as a manifestation of MS. Baseline spasticity scores ranged from 2 to 4 on the Penn Spasm scale and from 0 to 3 on the Ashworth scale. Nine of the 11 patients were female, and the mean age was 41.0 years (range, 21-55 years). Half of the patients were treated with levetiracetam as monotherapy for spasticity, and half received 1 to 3 additional drugs for spasticity, in combination with levetiracetam (Table). In addition, all patients were receiving a variety of other medications for treatment of MS or other concomitant disorders.

All patients started levetiracetam therapy at a dose of 250 mg daily. The dose was titrated during a period of 2 to 4 weeks, up to a dose of 3000 mg or less daily. The final mean ± SD dose was 1583.3 ± 633.7 mg daily. Patients were treated with levetiracetam for 1 to 4 months, with a mean time of 3.2 months between the baseline and follow-up evaluations.

All patients experienced a decrease in Penn Spasm score between the baseline and follow-up evaluations (Table). The mean ± SD Penn Spasm score was 2.7 ± 0.65 and the median score was 3.0 at baseline and decreased to 0.9 ± 0.29 and 1.0 at follow-up, reflecting a decrease in phasic spasticity. Ashworth scores did not change from baseline to follow-up (mean of 1.3 and median of 1.0 scores). In addition to improvements in phasic spasticity, 3 patients incidentally reported improvements in neuropathic pain that had been present at baseline.

Five of the 12 patients reported an adverse event during levetiracetam treatment. Two patients reported drowsiness, and 1 patient each reported nausea, constipation, and edema. The edema resolved with discontinuation of the drug, and the dose was reduced in 1 patient who reported drowsiness.
Levetiracetam was effective in reducing phasic spasticity in all patients in our retrospective medical record review. Similar to our clinical experience with gabapentin, we did not detect any changes in tonic spasticity as a result of levetiracetam treatment.

Three patients also reported improvements in neuropathic pain. Antiepileptics have been used to treat neuropathic pain in a variety of clinical conditions, including postherpetic neuralgia and diabetic neuropathy, but large, placebo-controlled double-blinded studies of neuropathic pain in patients with MS have not been reported, to our knowledge.10,19 Our incidental findings coincide with the results of a small, open-label trial of levetiracetam in patients with neuropathic pain due to a variety of causes. These patients did not obtain adequate pain relief when treated with gabapentin alone but did report substantially improved pain relief when levetiracetam was added to the regimen.10 Although a decrease in pain may affect the degree of spasticity, only the spasm score was affected while the modified Ashworth score remained the same.

Levetiracetam was well tolerated in our patient group. The 5 adverse events reported were generally mild and did not require drug discontinuation, with the exception of edema in 1 patient. Although cognitive function was not monitored prospectively, no adverse cognitive effects were spontaneously reported.

The currently established safety and pharmacokinetic profiles of levetiracetam suggest that it may be well tolerated in MS patients who typically require treatment with a multitude of drugs, thereby placing them at risk for drug interactions and adverse events, including cognitive dysfunction. In our retrospective analysis, levetiracetam was effective as well as safe for the treatment of phasic spasticity in patients with MS. A placebo-controlled, blinded clinical trial is needed to confirm these preliminary findings.

Accepted for publication August 19, 2003.

Author contributions: Study concept and design (Drs Hawker and Frohman); acquisition of data (Drs Hawker, Frohman, and Racke); analysis and interpretation of data (Drs Hawker and Frohman); drafting of the manuscript (Drs Hawker and Frohman); critical revision of the manuscript for important intellectual content (Drs Hawker, Frohman, and Racke); obtained funding (Dr Hawker); administrative, technical, and material support (Drs Hawker and Frohman).

Partial funding for this study was provided by UCB Pharma Inc, Brussels, Belgium.

We acknowledge Sciena Healthcare Education, Durham, NC, for assistance with manuscript preparation.

Corresponding author: Kathleen Hawker, MD, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Room J3.134, Dallas, TX 75390-9036.

Changes in Penn and modified Ashworth spasticity scores.