Levetiracetam in Tardive Dyskinesia: An Open Label Study

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Abstract: **Levetiracetam (LEV), a novel antiepileptic drug, has demonstrated antidyskinetic effect in preclinical animal models of Parkinson's disease (PD) and in one open label study in PD patients with levodopa-induced dyskinesia. The acute antidyskinetic effects of LEV in patients with tardive dyskinesia were evaluated in an open label study. Eight patients received oral LEV (1,000 mg/day) for 1 month and blinded evaluations were performed at baseline and at the end of the treatment period. A significant reduction of the abnormal movements was recorded while psychiatric symptoms did not worsen and the adverse event profile was benign. LEV may be efficacious for the treatment of tardive dyskinesia and deserves further clinical testing.** © 2006 Movement Disorder Society

Key words: levetiracetam; tardive dyskinesia; antipsychotics

Levetiracetam (LEV) is a novel antiepileptic drug that appears to contrast with other anticonvulsants by involving a unique profile of activity[1] and the absence of significant drug interactions.[2] Some recent studies, however, indicate that LEV may play a role in the control of dyskinesias as well. LEV was found to reduce significantly levodopa-induced dyskinesia in parkinsonian monkeys without detrimental effects on the antiparkinsonian action of levodopa.[3–6] This effect was replicated in a small prospective open label pilot study in nine parkinsonian patients and in one case of a patient with tardive dyskinesia (TD).[7,8] In addition, piracetam, a related compound (levetiracetam is the S enantiomer of piracetam), has already been reported to produce also some improvement in TD symptoms.[9–11] Although its mechanism of action is not entirely defined, it seems that it prevents high-frequency neuronal firing and reduces hypersynchronization of neurons.[1] Therefore, LEV may have potential in reducing antipsychotic-induced tardive dyskinesia as well. The aim of this study was to evaluate the acute antidyskinetic effects of LEV in patients with antipsychotic-induced tardive dyskinesia.

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PATIENTS AND METHODS

The study was performed using an open label with blind assessment observational design. Eight consecutively chosen psychiatric outpatients (three men and five women) with psychosis and antipsychotic-induced tardive dyskinesia were prospectively recruited for participation. The inclusion criteria were as follows: adults from 18 to 65 years of age and diagnosis of tardive dyskinesia due to exposure to chronic antipsychotic treatment according to research diagnostic criteria for tardive dyskinesia outlined by Schooler and Kane[12] and in the DSM-IV.[13] The typical movements consistent with TD should be present for at least 6 months in the absence of any other causative neurological or general medical condition. Patients should be in stable psychiatric condition and cognitively competent in the judgment of the enrolling physician. All concurrent medications were maintained at constant doses for at least 1 month prior to study entry and throughout the duration of the study (Table 1). Exclusion criteria were as follows: acute medical illness; known adverse reaction to LEV or piracetam; female with the potential of becoming pregnant during the study; or renal disease (with creatinine clearance of less than 100 mL/min). All patients received oral LEV 500 mg twice a day for a 1-month period, while other medications were maintained at constant doses. The same blinded physician evaluated at baseline and at the end of the 1-month treatment period all patients enrolled. No information on the design of the study or about the drug tested was provided to the rater. He was not the treating physician of any of the patients enrolled, nor was he involved in any way in the care of those patients. He was unaware of the patient's diagnosis or current treatment, and he had no access to their medical charts. Patients were rated by means of the Abnormal Involuntary Movement Scale (AIMS), the Goetz Dyskinesia Scale, Clinical Global Impressions (CGI), and the Brief Psychiatric Rating Scale (BPRS). An ethics committee approved the protocol, and each patient provided written informed consent before inclusion in the study.

RESULTS

One patient dropped out of the trial after 4 days due to excessive sleepiness and sedation while seven completed the study and entered statistical analysis. No side effects, including somnolence, were reported by the other patients, either spontaneously or after specific questioning, except for one patient who complained for mild to moderate transient fatigue during the first week of treatment.

TABLE 1. *Patient characteristics*

Patient	Sex	Age	Diagnosis	Duration of disease (yr)	Concurrent medications (daily dose, mg)	Outcome
1	M	58	Schizophrenia	21	Perphenazine, 12; Amitriptyline, 30	
2	F	46	Schizoaffective disorder	14	Olanzapine, 10; Diazepam, 30	
3	F	56	Schizophrenia	22	Aloperidol, 25; Diazepam, 20	
4	M	59	Delusional disorder	7	Clozapine, 100	
5	F	58	Schizophrenia	29	Quetiapine, 1,000	
6	M	52	Schizophrenia	24	Risperidone, 6; Diazepam 15	
7	F	50	Schizophrenia	32	Clozapine, 200; Lorazepam, 6.25; Biperiden, 6	Dropout
8	F	62	Delusional disorder	5	Risperidone, 5; Lorazepam, 7.5	

After 1-month treatment with LEV at a dose of 1,000 mg/day, abnormal movements as measured with AIMS were significantly reduced from 15.8 ± 2.5 to 8.3 ± 2.3 (paired *t* test, $t = 6{,}778$; $P = 0.001$), or a mean reduction of 44%. In the Goetz Dyskinesia Scale, scores were reduced from 2.6 to 1.5 (Wilcoxon signed-rank test, $P = 0.026$), or a mean reduction of 44%, and in CGI, from 4.5 to 3.3 (Wilcoxon signed-rank test, $P = 0.031$), or a mean reduction of 26%. BPRS scores did not show significant changes during the study.

DISCUSSION

The results of this study provide preliminary evidence that LEV may be effective in the treatment of TD. The mechanism underlying the antidyskinetic effect of LEV in levodopa and antipsychotic-induced dyskinesias is elusive. As LEV possesses a significant ability to reduce neuronal hypersynchronization,[1] we can speculate that the antidyskinetic activity of LEV may relate to desynchronization of a possibly abnormal neuronal firing pattern of basal ganglia outputs, though this question deserves further electrophysiological investigations. There is also evidence that the drug may interfere with the development of the priming process.[3]

In a recent small prospective open label pilot study in nine PD patients with levodopa-induced dyskinesia, when LEV was added, *on* time with troublesome dyskinesia was reduced significantly from 23% to 10%, and *on* time without dyskinesia or with nontroublesome dyskinesia increased from 43% to 59%, without worsening of parkinsonism.[7] Somnolence was the most troublesome side effect, accounting for a 33% dropout rate. Interestingly, another recent open label study in parkinsonian patients with levodopa-induced dyskinesia failed to reproduce these findings and was also associated with a high incidence of dropouts due to somnolence (50%).[14] Those differences in efficacy could be attributed to the different study designs followed by the two studies: the study by Zesiewicz and colleagues[7] used mainly data from patient diaries collected every 10 days, while the study by Meco and colleagues[14] used monthly UPDRS physician's ratings as well as diary data.

A particular advantage of LEV is its wide therapeutic index, its relatively minimal neurotoxic effects, and the absence of significant drug interactions.[2] In the treatment of epilepsy, somnolence is reported as a side effect in 10% of patients.[15] Indeed, in our study, troublesome side effects were practically absent, with the exception of one patient withdrawing early due to somnolence. The rest did not report any significant adverse reactions. The higher incidence of daytime somnolence reported in parkinsonian patients is probably due to the more advanced age of parkinsonian patients, with a mean age of patients in the Parkinson studies of 65 years, comparing to a mean age of 55 years in our study. In addition, pharmacological interactions with L-dopa and dopamine agonists could have additive effects with LEV in sleepiness, while the contribution of Parkinson's disease itself cannot be ignored. Interestingly, "mild to moderate bradykinesia and rigidity" was recorded in the chart of the only patient in our study who experienced excessive somnolence and dropped out. Also, it may be worth noting that he was the only patient receiving an anticholinegic (biperiden, 6 mg/day), although in a relatively low dose, for excessive salivation.

This study is limited in that it is a pilot study using an open label design, a small number of subjects, and a short duration of drug administration. Nevertheless, treatment response suggests that LEV may be a well-tolerated drug that does effectively control neuroleptic-induced dyskinesias. Larger randomized placebo-controlled studies to assess the safety and efficacy of LEV in patients with tardive dyskinesia should be considered to evaluate further this promising therapy.

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Use of Antiparkinsonian Drugs in Denmark: Results from a Nationwide Pharmacoepidemiological Study

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Abstract: **The objective of the present study was to record the use of antiparkinsonian drugs (APD) in Denmark and discuss estimates of the incidence and prevalence rates of Parkinson's disease (PD). The main indication for treatment with APD is idiopathic PD. The use of APD is, therefore, an indicator of the epidemiology of PD and Parkinsonism. We used a drug tracer design, which previously has been found applicable in estimating the frequency of PD. From a national prescription database, all persons who purchased APD from 1995 to 2002 could be identified on an individual level. Results show an age-standardized prevalence rate for APD purchase of 164.0 persons per 100,000, and an incidence rate of 55.9 persons per 100,000. The total number of persons purchasing APD was 11,656 per year on average. Our results showed higher figures of persons purchasing APD than the estimated prevalence of idiopathic PD in Denmark, which is approximately 100 persons per 100,000, corresponding to 5,000 to 6,000 persons. The differences might in part be explained by other indications for APD prescription in addition to PD and in part by misdiagnosis. However, the possibility of somewhat higher incidence and prevalence rates of PD than hitherto estimated should be considered.**

Key words: Parkinson's disease; epidemiology; levodopa; prescription database;

The incidence and prevalence rates of Parkinson's disease (PD) have been estimated in many studies, and figures vary greatly.[1–3] The variations are mostly attributed to different study designs but also to features related to age, sex, geography, ethnicity, and environmental

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