Comparison of Cognitive Effects of Lamotrigine and Oxcarbazepine in Epilepsy Patients

Jong-Geun Seo, M.D., Da-In Lee, M.D., Yang-Ha Hwang, M.D., Ho-Won Lee, M.D., Doo-Kyo Jung, M.D., Ph.D., Chung-Kyu Suh, M.D., Ph.D., Soon-Hak Kwon, M.D., Ph.D.*, Sung-Pa Park, M.D., Ph.D.

*Department of Neurology and *Pediatrics, School of Medicine, Kyungpook National University, Daegu, Korea*

Background and Purpose: This study compared the cognitive effects of 1 year of treatment with lamotrigine (LTG) and oxcarbazepine (OXC) in epilepsy patients.

Methods: This retrospective study investigated 60 epilepsy patients undergoing neuropsychological tests who were either newly diagnosed or untreated in the preceding 6 months. The cognitive function in 30 patients receiving LTG monotherapy and 30 age-matched patients receiving OXC monotherapy was compared after 1 year. The neuropsychological scores at baseline and all of the epilepsy-relevant variables except seizure type did not differ between the groups. The mean daily dosages of LTG and OXC at 1 year were 93 mg and 825 mg, respectively.

Results: The posttreatment list-learning performance was better in the LTG group than in the OXC group ($p<0.05$). The incidence of cognitive complaints did not differ between the two groups. The list-learning performance and Trail Making Test scores were better in each group after treatment.

Conclusions: LTG and OXC monotherapies have similar, slightly beneficial effects on cognitive function, and are probably not harmful.

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Key Words : Adverse effects, Cognition, Lamotrigine, Oxcarbazepine

INTRODUCTION

Cognitive and behavioral deficits are more common in patients with epilepsy than in the general population.[1] A significant proportion of patients with epilepsy are at increased risk of cognitive impairment due to various factors.[1] Moreover, antiepileptic drugs (AEDs) can cause adverse cognitive effects.[2,3] AEDs exert a dosage-dependent effect on cognitive function, and AED polytherapy can frequently result in worse cognitive side effects. The cognitive effects of traditional AEDs in monotherapy and as adjuncts to other drugs are relatively well established,[3] but the differential effects of new AED monotherapies are less clear.[3]

Lamotrigine (LTG) is an AED with wide spectrum efficacy in the treatment of partial seizures and primary and secondary generalized seizures.[4] However, the cognitive effects of LTG in patients with epilepsy are not easy to interpret. For example, it is difficult to isolate the genuine effects of LTG from the cognitive changes caused by changes in seizure frequency. Even in patients with a low seizure frequency, it appears to be difficult to interpret the cognitive effects of LTG because

Received : October 31, 2006 / Accepted : January 16, 2007 / Address for correspondence : Sung-Pa Park, M.D., Ph.D.
Department of Neurology, School of Medicine, Kyungpook National University 50 Samduk 2-Ga, Joong-Gu, Daegu, 700-721, Korea
Tel: +82-53-420-5769, Fax: +82-53-422-4265, E-mail: sppark@mail.knu.ac.kr
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LTG may suppress epileptiform EEG discharges, which also may result in changes to cognitive function.[5,6]

Studies comparing LTG with other AEDs in healthy volunteers have revealed fewer side effects on cognitive function for LTG than for carbamazepine (CBZ), valproate (VPA), and topiramate.[6–9] Moreover, short-term treatment of normal volunteers with a low dosage of LTG resulted in improved cognitive activation as quantified by simple reaction-time measurements.[6] Thus, further neuropsychological studies are needed to elucidate the cognitive effects of LTG in patients with epilepsy, including in those on longer maintenance periods.

Oxcarbazepine (OXC) is a novel AED that is chemically related to CBZ and is approved as an initial or add-on treatment for partial seizures.[10] Two European studies have evaluated its cognitive effects in adult epilepsy patients.[10,11] In one of these, newly diagnosed patients received OXC or other AEDs as a monotherapy for 4 months. Compared with baseline, OXC-treated patients improved in 1 of 20 cognitive tasks and worsened in none, and the results were similar in patients receiving CBZ, VPA, phenobarbital, or phenytoin (PHT) monotherapy.11In the other study, which was a double-blind comparison of OXC with PHT monotherapy in newly diagnosed patients,[12] no differences between OXC and PHT were detected in any of the seven cognitive variables measured at any of the time points. We have also previously investigated the cognitive effects of OXC in epilepsy patients using neuropsychological tests and event-related potentials, and found no negative effects on cognition after 1 year of treatment with OXC.[13] The results of these studies suggest that OXC does not affect cognitive function in epilepsy patients.

This study compared the cognitive effects of 1 year of treatment with LTG and OXC in epilepsy patients. The results of various cognitive tests and subjective complaints were compared at baseline and after 1 year of medication between the two groups.

MATERIALS AND METHODS

1. Subjects

Six years ago, our epilepsy clinic began to study the cognitive effects of AEDs on epilepsy patients, routinely conducting cognitive evaluations on the basis of self-reporting, subjective complaints, and various cognitive tests before and after treatment with AEDs. Symptom severity after medication was divided into four grades: grade 0, no symptoms; grade 1, mild and intermittent cognitive problems, sometimes forgotten; grade 2, moderate and steady cognitive deficits, sometimes discomforting; and grade 3, severe cognitive deficits making the patient unable to continue medication. Cognitive tests were performed three times in each subject: at baseline, and 1 year and 3 years after starting medication. EEGs were measured in all patients when they entered the study and also at the time of the second and third cognitive tests. An MRI study of the brain was performed once in each patient during the study.

Our epilepsy neuropsychological database contained more than 600 cases, from which we randomly selected cases that conformed with all of the following criteria: (1) LTG or OXC monotherapy with follow-up cognitive evaluations performed at 1 year, (2) newly diagnosed epilepsy or epilepsy that had not been treated with AEDs within at least the previous 6 months, (3) no progressive neurological disorders, head injury, mental retardation, alcohol or drug abuse, ongoing use of any centrally acting medications, severe psychiatric problems, or other severe medical disorders, and (4) no cognitive complaints at baseline even in the absence of the above insults.

A total of 30 patients for the LTG group and 30 age-matched patients for the OXC group who met the above criteria were collected from the database. The characteristics of the patients are listed in Table 1. The daily mean AED dosages at 1 year were 93 mg for LTG and 825 mg for OXC. The monthly seizure rate decreased significantly in both groups after AED medication. None of the epilepsy-relevant variables except seizure type differed between the groups.

Table 1. Patient characteristics

	LTG (n=30)	OXC (n=30)	Significance[a]
Age, y, mean (range)	26.4 (15-53)	28.7 (14-53)	NS*
Sex, % male	43	53	NS
Education, %			
graduate primary or middle school	13	20	NS
graduate high school or college	87	80	NS
Seizure type, %			$P < 0.01$
Partial	33	77	
Generalized	67	23	
Duration of epilepsy, y, mean (range)	3.6 (0.1-20)	3.1 (0.1-20)	NS
Newly diagnosed epilepsy, within 3 months, %	73	60	NS
Presence of brain pathology in MRI, %	17	30	NS
Dose at 1 year, mg/day, mean (range)	93 (50-200)	825 (600-1,500)	
Seizure rate for recent 3 months, seizures/month			
Baseline	0.5 (0.3-3)	1.7 (0.3-20)	NS
At 1 year	0.1‡ (0-1)	0.5† (0-8)	NS
Abnormality of EEG, %			
Baseline	43	57	NS
At 1 year	23	33	NS

LTG; lamotrigine, OXC; oxcarbazepine

[a]Fisher exact tests and t tests for independent samples (two-sided), *Nonsignificant, $P > 0.05$, †$P < 0.05$, ‡$P < 0.01$, comparing with baseline

2. Neuropsychological tests

All cognitive tests were administered in a sound-attenuated, temperature-controlled room by a single examiner. According to the literature and our own clinical experience, we selected two cognitive measures that were particularly sensitive to AED-induced cognitive impairment. We assessed memory function through list learning, immediate and delayed word recall, word recognition, and visual reproduction based on the Memory Assessment Scale, which was obtained from Psychological Assessment Resources.[14] We assessed attention deficit by using digit spans (forward and backward) from the Wechsler Memory Scale–Revised.[15] We examined attention, visuomotor tracking abilities, and mental flexibility with the Trail Making Test (TMT) from the Halstead-Reitan Battery.[16] We studied verbal fluency using semantic fluency tests from the Boston Diagnostic Aphasia Examination–Third Edition.[17] Testing sessions lasted about 30 minutes. If seizures occurred during a neuropsychological examination, the test was suspended and the data discarded.

3. Study design

We evaluated the differences in cognitive function between the LTG and OXC groups at 1 year based on subjective complaints and cognitive tests. We also investigated the changes in cognitive scores from baseline to those after 1 year of medication in each group. We compared cognitive results with the patient characteristics, the clinical features of the epilepsy, EEG abnormalities, neuroradiological findings, and daily AED dosage. To assess the effects of daily AED dosage on cognitive function, the frequency of cognitive complaints and the change in cognitive scores from baseline to those after 1 year of medication (at each target dosage) were compared.

4. Statistical analysis

Higher scores indicated better performance on all cognitive tests except the TMT (parts A and B), for which higher scores indicate a poorer performance because the time required was defined as the dependent

Table 2. Neuropsychological outcome

Measure	Test session	LTG (*n*=30) mean (SD)	OXC (*n*=30) mean (SD)	Significance[a]
List learning	Baseline	61.7 (6.6)	59.3 (7.3)	NS*
	At 1 year	65.0 (4.3)‡	61.5 (7.2)†	$P < 0.05$
Immediate word recall	Baseline	11.5 (1.1)	11.1 (1.4)	NS
	At 1 year	11.6 (0.7)	11.2 (1.1)	NS
Delayed word recall	Baseline	11.5 (1.2)	11.1 (1.2)	NS
	At 1 year	11.6 (0.6)	11.3 (1.0)	NS
Word recognition	Baseline	12.0 (0.0)	11.9 (0.3)	NS
	At 1 year	12.0 (0.0)	12.0 (0.0)	NS
Visual reproduction	Baseline	8.9 (1.4)	8.3 (2.1)	NS
	At 1 year	8.8 (1.5)	8.3 (1.6)	NS
Digit span, forward	Baseline	9.1 (2.3)	8.5 (2.4)	NS
	At 1 year	8.9 (2.0)	8.3 (2.5)	NS
Digit span, backward	Baseline	6.9 (2.3)	7.1 (2.7)	NS
	At 1 year	7.0 (2.4)	7.4 (2.6)	NS
Trail Making Test, part A				
Time (sec)	Baseline	30.8 (8.7)	29.7 (17.1)	NS
	At 1 year	24.4 (7.7)‡	24.4 (13.8)†	NS
Error no.	Baseline	0.2 (0.5)	0.1 (0.3)	NS
	At 1 year	0.2 (0.6)	0.1 (0.2)	NS
Trail Making Test, part B				
Time (sec)	Baseline	75.4 (29.1)	78.2 (48.7)	NS
	At 1 year	72.3 (29.8)	66.4 (39.5)†	NS
Error no.	Baseline	0.9 (1.1)	0.6 (0.9)	NS
	At 1 year	0.8 (0.9)	0.4 (0.7)	NS
Verbal fluency	Baseline	17.0 (5.6)	15.1 (4.6)	NS
	At 1 year	17.3 (5.2)	16.7 (5.2)	NS

LTG; lamotrigine, OXC; oxcarbazepine

[a]*t* test for independent samples (two-sided), *Nonsignificant, $P > 0.05$, †$P < 0.05$, ‡$P < 0.01$, paired *t* test for comparison with baseline
Higher scores indicate better performance except for Trail Making Test

measure for these tests. The data for continuous variables are expressed as mean±SD values, and the data for categorized variables are expressed as frequencies. We used paired *t*-tests to compare cognitive scores before and after medication in the same subject. We also used *t*-tests for independent samples to compare the cognitive scores between the LTG and OXC groups. Fisher's exact test was used for the categorized variables. A one-way analysis of variance for independent samples was used for comparing differences in cognitive scores before and after AED medication among groups with different AED dosages. Bonferroni correction was employed for post-hoc comparisons, with the α level set at 0.05.

RESULTS

1. Intra- and intergroup differences

Table 2 indicates that in the LTG group, the list-learning performance and score for TMT part A were better at 1 year than at baseline (both $p<0.01$). In the OXC group, the list-learning performance and scores for TMT parts A and B were also better at 1 year than at baseline (both $p<0.05$).

The results of several neuropsychological tests performed at baseline were compared between the patient groups. As indicated in Table 2, the initial cognitive scores did not differ significantly. However,

after 1 year of treatment, the list-learning performance was better in the LTG group than in the OXC group (p<0.05).

The incidence of cognitive complaints did not differ significantly between the OXC group (7/30 patients, 23%) and the LTG group (6/30 patients, 20%). Twenty percent of the patients taking LTG were described has having only a memory deficit, which was categorized as grade 1. Twenty percent of patients taking OXC complained of memory deficit, with 3% complaining of an attention or concentration deficit, which were also categorized as grade 1.

2. Correlation analyses

The frequency of cognitive complaints and changes in neuropsychological test scores in the LTG and OXC groups were not correlated with patient characteristics, clinical features of epilepsy, EEG abnormalities, neuroradiologic findings, or daily AED dosage.

DISCUSSION

This was a comparative study that compared the cognitive effects of 1 year of treatment of LTG and OXC in epileptic patients. The posttreatment list-learning performance was better in the LTG group than in the OXC group. The incidence of cognitive complaints did not differ between the two groups. The list-learning performance and TMT scores were better in each group after AED treatment.

Even though several studies have provided clinical evidence of the effects of LTG on cognitive function, their findings were limited by the small numbers of patients, the absence of baseline cognitive assessments, and the presence of intractable seizures, irregular dosages, concurrent or previous AED use, and brain pathology.[6–9,18,19] To minimize these confounding factors, the ideal cognitive study should administer an AED monotherapy to patients with newly diagnosed epilepsy, with cognitive assessments performed at baseline, before treatment, and at a point when the patients have been in steady-state treatment at a fixed clinical dosage.[20,21] Our cases met these criteria, and we also reduced several of the confounding factors in epilepsy. Moreover, all of our patients were receiving a monotherapy, many of them were newly diagnosed and nonlesional, and most of them were well controlled by AED.

Comparative methodologies are also popular in studies of the cognitive effects of AEDs, in which these effects of the drug under investigation are compared with those of other widely prescribed drugs. Since our study was retrospective, it did exhibit some inevitable methodological limitations as a comparative study. Patients were selected from our neuropsychological database according to a set of self-generated inclusion criteria, and thus selection bias cannot be excluded. Therefore, multicenter, double-blind, placebo-controlled studies still need to be performed.

The reasons for the positive effects of AEDs on cognition relate to their therapeutic effects on epilepsy, leading to a reduction in psychosocial problems or the stimulation of psychomotor functioning.[1–3,22] Animal experiments suggest that LTG has no effect on either the induction or the maintenance of long-term potentiation of memory function,[23] and may even protect against excitotoxic and ischemic insults.[24] Because LTG does not primarily act on GABAergic neurotransmission, it may be associated with less cognitive and behavioral impairment.[25] Furthermore, LTG has demonstrated efficacy in bipolar disorder in terms of preventing or delaying mood episodes in depression, which is a mainstay psychosocial problem in epilepsy.[26] Therefore, LTG may also had positive effects on cognition. Unfortunately, we did not conduct neuropsychological tests related to mood state in our study, and hence were unable to assess mood changes that were directly attributable to LTG. Another possible reason for improved cognitive scoresis the use of low-dosage LTG in our patients. We administered low-dosage LTG for monotherapy (50-200 mg/day) in patients with newly diagnosed epilepsy or epilepsy that had not been treated with AEDs. Because cognitive adverse effects of AEDs have been related to the administration of higher dosages, our use of low-dosage LTG may have contributed to the improved cognitive scores. However, we found no correlation between changes in cognitive

scores and the dosage used. The last possible reason for cognitive improvement is the existence of practice effects, despite the long test-retest interval used in this study. However, only two of the ten categories in the cognitive tests were significantly changed at retest, and practice effects would have been evident in most of the measures used.[27] Testing a control group at the same time intervals might have solved this problem.

Treating epilepsy may reduce the cognitive and behavioral impairments by stopping or decreasing the seizures, but it may also induce undesirable effects on cognition and behavior. The optimal epilepsy treatment involves using an AED that best controls the patient's seizures with the fewest side effects. Cognitive effects are only one factor in AED selection, since AED-induced cognitive impairments may be outweighed by the potential for seizure control and overall improvement in quality of life. The harmful cognitive effects of AEDs are especially important to those who require maximal cognitive efficiency for their job, school, or daily activities. Our study demonstrated that LTG and OXC monotherapies have similar, slightly beneficial effects on cognitive function, and are probably not harmful after 1 year of medication. However, future prospective studies are needed to confirm the cognitive effects of LTG and OXC in epilepsy patients.

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