Regional Effects of Lamotrigine on Cerebral Glucose Metabolism in Idiopathic Generalized Epilepsy

Eun Yeon Joo, MD; Woo Suk Tae, MS; Seung Bong Hong, MD, PhD

Background: Antiepileptic drugs have been reported to affect cerebral metabolism. We performed $^{18}$F-fluorodeoxyglucose positron emission tomography (PET) before and after lamotrigine administration to investigate its effects on cerebral glucose metabolism in patients with drug-naive idiopathic generalized epilepsy.

Design: We included patients who were newly diagnosed as having idiopathic generalized epilepsy or who had not taken an antiepileptic drug after the diagnosis was made. Antiepileptic drug $^{18}$F-fluorodeoxyglucose PETs were obtained before and after lamotrigine administration in 21 subjects (male-female ratio, 10:11; mean±SD age, 24.3±2.8 years). The mean lamotrigine dosage was 211.9 mg/d (range, 175.0-275.0 mg/d). For statistical parametric mapping analysis, all PET images were spatially normalized to the standard PET template and then smoothed using a 14-mm full width at half-maximum gaussian kernel. The paired t test was used to compare premedication and postmedication $^{18}$F-fluorodeoxyglucose PET images.

Results: After lamotrigine administration, cerebral metabolism was decreased in bilateral thalami, bilateral caudate nuclei, the left side of the putamen, the left entorhinal area, bilateral parahippocampal gyri, the right inferior temporal gyrus, the left rectosubcallosal gyrus, bilateral superior frontal gyri, the left precentral gyrus, left pericentral gyrus, the right superior parietal lobule, and bilateral substantia nigra at $P<.05$ corrected for multiple comparisons using the false discovery rate approach. No brain region showed increased metabolism after lamotrigine administration.

Conclusion: This study revealed that lamotrigine treatment reduces glucose metabolism in the thalamus, basal ganglia, and multiple regions of the cerebral cortex in drug-naive patients with idiopathic generalized epilepsy.

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The effect of antiepileptic drugs (AEDs) on global cerebral glucose metabolism may be associated with their mode of action and their effects on cognitive performance. Antiepileptic drugs lower cerebral glucose metabolism, which may be associated with cognitive impairment. Valproate depressed global cerebral metabolism to a greater degree than did carbamazepine and phenytoin, but less than did phenobarbital. Theodore et al suggested that different AEDs affected the brain metabolism at different levels, but that they had no region-specific cortical effects. They interpreted those findings because of the AED effects on ubiquitous sodium ion channel or the γ-aminobutyric acid neurotransmitter system. Regional and global changes were observed after vigabatrin or valproate administration in the quantitative cerebral blood flow studies. Idiopathic generalized epilepsy (IGE) is characterized by typical absences, tonic-clonic seizures, and myoclonic jerks. Patients with IGE manifest all or some of these seizure types. It has been traditionally held that there is no radiological abnormality in patients with IGE, but sophisticated image processing and quantitative magnetic resonance imaging (MRI) studies suggested that, in some cases, there may be a subtle structural abnormality. Significant hemodynamic changes in bilateral thalamic and cortical areas were observed during generalized spike and wave or polyspike and wave bursts in a functional MRI study of patients with IGE. These findings may provide evidence for the key role of the thalamocortical networks in the pathogenesis of generalized epilepsy.

To our knowledge, lamotrigine, one of the new AEDs affecting cerebral glucose metabolism, has not been previously ex-
amined. Lamotrigine is frequently prescribed as monotherapy and has shown good efficacies in adolescents and adults who are newly diagnosed as having either partial or mixed seizure disorders in large comparative or dose-controlled trials.11,12

The antiepileptic effect of lamotrigine has been attributed to the inhibition of voltage-dependent sodium channels and a consequent inhibition of transmitter glutamate release.13,14 However, the mode of action of lamotrigine has been studied only in short-term animal experiments or in vitro.13-15

To evaluate the in vivo effects of lamotrigine on cerebral glucose metabolism, we recruited new-onset or drug-naive patients with IGE who experienced either generalized tonic-clonic or myoclonic seizures to exclude the regional effect of partial epilepsy on cerebral glucose metabolism; we also performed 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) before and after lamotrigine monotherapy. The region of interest—based methods used in previous studies16 analyzed only brain regions included in predetermined regions of interest, and did not involve white matter. To investigate drug effects over the whole brain, including gray and white matter, statistical parametric mapping (SPM) analysis was performed on FDG-PET images before and after lamotrigine therapy.

**METHODS**

**PATIENTS**

We enrolled patients who visited the epilepsy clinic of the Samsung Medical Center from December 17, 2001, to November 20, 2004, and were diagnosed as having new-onset or drug-naive IGE. The inclusion criteria were as follows: (1) those with clinically documented generalized tonic-clonic seizures, with or without myoclonic seizures; (2) those with no history of antiepileptic medication administration; (3) those with no lesion by brain MRI; and (4) those with no focal epileptiform discharges by electroencephalography. Patients with a history of head trauma, other neurologic disease, or psychiatric disorders or those taking a drug that might have affected regional cerebral glucose metabolism were excluded.

Twenty-seven patients with epilepsy underwent an FDG-PET study before lamotrigine administration. During the 16-week period of lamotrigine treatment, 2 patients dropped out. Of the remaining 25 patients, 4 (16%) still experienced seizures after 4 months of lamotrigine treatment, although their seizure frequencies were decreased (mean seizure reduction rate of these 4 patients, 58%; rate range, 20%-80%). Twenty-one (84%) of the 25 patients became seizure free after the 16-week period of lamotrigine treatment. Finally, 21 patients treated with lamotrigine underwent an FDG-PET study after treatment completion.

All patients were informed of the procedure and the potential risks of FDG-PET and agreed to voluntarily participate. Informed consent in accord with the guidelines of the institutional review board at Samsung Medical Center was obtained from all subjects.

**STUDY DESIGN**

Each patient received lamotrigine monotherapy for 16 to 20 weeks. Before lamotrigine treatment, all subjects underwent a physical examination, a routine blood test (including a hematology and chemistry panel, which included liver function tests), and brain MRI. The predetermined target dosage for lamotrigine was 200 mg/d, although this varied depending on the individual. Lamotrigine dosages were gradually increased to 200 mg/d over an 8-week titration period. Lamotrigine was given at 25 mg/d for the first 2 weeks and at 50 mg/d for the second 2 weeks. From the fifth week, lamotrigine was increased by 50 mg/d each week so that patients reached 200 mg/d at the seventh or eighth week. If seizures recurred after the 8-week titration period, lamotrigine dosages were further increased by 25 mg/d each week to achieve a seizure-free state of at least 8 weeks before the postlamotrigine FDG-PET study. All patients were scheduled to receive an increasing daily dose to 200 mg. However, if a patient complained of intolerable adverse events because of lamotrigine administration, the lamotrigine dosage was decreased by 25 mg/d each week until the symptoms subsided. During the lamotrigine administration period, patients were subject to have a physician’s examination once every 2 weeks; blood testing for hematology and liver function was performed twice before medication administration and again at the end of the study period. Physicians confirmed seizure frequency in a seizure diary whenever a patient visited the outpatient clinic.

**FDG-PET IMAGING PROCEDURE**

18F-fluorodeoxyglucose PET images were obtained before and after lamotrigine treatment using a scanner (GE Advance PET scanner; GE Medical Systems, Milwaukee, Wis). Patients fasted for 4 hours or longer and were then given an intravenous injection of FDG, 7 to 10 mCi (260-370 MBq). The FDG-PET studies were performed more than 24 hours (range, 7-115 days in our patients) after the last seizure. The number and date of seizure occurrence were recorded in a seizure diary by a patient or caregiver. Electroencephalographic monitoring during the FDG uptake period (postinjection, approximately 0-30 minutes) demonstrated no electroencephalographic seizure activity and confirmed wakefulness in each subject. PET images were reconstructed using a Hanning filter (cutoff frequency, 4.5 mm) and were displayed as a 128 × 128 matrix (pixel size, 1.95 × 1.95 mm, with 35 slices of thickness at 4.25 mm). Attenuation correction was performed using a standard calculated method with a series of ellipses.16 All studies were conducted in a quiet, dimly lit environment with minimal background noise.

**SPM ANALYSIS OF FDG-PET IMAGES**

18F-fluorodeoxyglucose PET images obtained before and after lamotrigine treatment were processed using a multipurpose math analysis package (MATLAB 6.5; The MathWorks, Inc, Natick, Mass) incorporated into computer software (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, University of London, London, England).17 Before the spatial normalization of FDG-PET images obtained before and after lamotrigine treatment to a standard FDG-PET template, FDG-PET images obtained after lamotrigine treatment were linearly transformed to match FDG-PET images obtained before lamotrigine treatment. By using this registration, PET images obtained after lamotrigine treatment could be correctly registered to PET images obtained before lamotrigine treatment. Paired FDG-PET images obtained before and linearly transformed after lamotrigine treatment were spatially normalized into a standard PET template, provided in the computer software (SPM99) to remove intersubject anatomical variability.18 A 12-parameter affine and a nonlinear transformation were per-
formed to register FDG-PET images to the standard PET template. Spatially normalized images were then smoothed by convolution using an isotropic gaussian kernel with a 14-mm full width at half maximum to increase the signal-noise ratio and to account for subtle variations in anatomical structure. The accuracy of the spatial normalization was checked using a cross-registration function. The count of each voxel was normalized to the total count of the brain (proportional scaling) to remove differences in global cerebral glucose metabolism between individuals. After spatial and count normalization, the paired t test was used to perform group comparisons on FDG-PET images before and after lamotrigine treatment. The height threshold was set to $P < .05$ corrected for multiple comparisons using the false discovery rate (FDR) approach. The extended threshold was $k_f > 125$. The FDR correction was performed using the FDR toolbox (http://www.sph.umich.edu/~nichols/FDR). Results were displayed on the 2-dimensional planes of a healthy subject's MRI template after spatial normalization.

**RESULTS**

**CLINICAL INFORMATION**

Twenty-one patients (10 males and 11 females) had FDG-PET scans before and after lamotrigine treatment. The mean±SD age of epilepsy onset was 19.3±1.7 years (range, 15-21 years), and the mean age at FDG-PET scanning was 24.3 years (range, 16-27 years). Based on history, seizure types were generalized tonic-clonic seizures in 16 patients and a myoclonic seizure with or without generalized tonic-clonic seizures in 5 patients. The mean±SD seizure frequency of the patients was 3.5±4.9 per month (range, 1-15 per month). Interictal electroencephalography showed generalized spike-wave mixtures with bifrontal maximum in 12 patients and generalized spikes in 9 patients. None of the patients showed focal epileptiform discharges. No patients showed evidence of structural lesions or abnormal findings in brain MRIs.

**LAMOTRIGINE DOSAGE REGIMEN AND TREATMENT DURATION**

Of the 21 patients, 14 (67%) achieved a seizure-free state at 200 mg/d from the eighth treatment week. Five patients experienced habitual generalized tonic-clonic seizures at a lamotrigine dosage of 200 mg/d. Three of these patients became seizure-free at 250 mg/d and the other 2 at 275 mg/d. The other 2 patients were seizure-free at 200 mg/d and had been seizure-free from medication commencement, but required dose reduction to 175 mg/d because of gastrointestinal discomfort or a floating sensation without seizure recurrence. All patients who had FDG-PET scans before and after lamotrigine treatment achieved a seizure-free state by taking a mean±SD of 211.9±29.1 mg/d and did not experience a serious adverse event.

**SPM ANALYSIS OF FDG-PET IMAGES**

The SPM analysis showed significantly ($P = .03$ to .04) reduced regional cerebral glucose metabolism after lamotrigine administration in corticobasal ganglia-entorhinal areas. Cerebral metabolism was reduced in bilateral thalami, bilateral heads of the caudate nuclei, the left side of the putamen, the left entorhinal area, bilateral parahippocampal gyri, the right inferior temporal gyrus, the left rectus/supracallosal gyrus, bilateral superior frontal gyri, the left middle frontal gyrus, the right precentral gyrus, the left pericentral gyruis, the right superior parietal lobule, and bilateral substantia nigra (Table and Figure). Significance was set at an FDR-corrected $P < .05$. No brain area showed increased glucose metabolism after lamotrigine treatment.

**COMMENT**

In the present study, we investigated the effects of lamotrigine on cerebral glucose metabolism in drug-naive patients with IGE.

Hypometabolism occurring after lamotrigine treatment was observed primarily in the striatum (caudate nuclei and putamen), substantia nigra, and the temporal cortices, including the entorhinal areas. The basal ganglia have also been suggested to play a role in the initiation and propagation of seizure activity. The striatum is the receptive component of the basal ganglia and receives input from the cerebral cortex. The substantia nigra, one of the basal ganglia control circuit, is reciprocally connected with the striatum. In an in vitro electrophysiological study conducted with rats, lamotrigine was determined to preferentially inhibit corticostriatal excitatory glutamatergic transmission, by modulating multiple sites of action within the striatum. The substantia nigra has been identified as a critical site to play a significant role in the generation and propagation of generalized seizures. Recently, the animal study using electrocorticography and multunit recordings in freely behaving rats showed that at the beginning of the absence seizure, the firing rate in substantia nigra pars reticulata increased significantly, and before the end of the seizure, the firing rate decreased progressively. Those findings supported the concept that nigral control mechanisms are involved in modulating the propagation of an ongoing generalized seizure. Lamotrigine was also reported to reduce the rates of glutamate neurotransmitter release at synapses within the entorhinal cortices of rats, thus inducing an antiepileptic effect. After vigabatrin administration, hypometabolism was most prominent in the right inferior lateral and bilateral medial temporal regions. Decreases of regional metabolism and cerebral blood flow in medial temporal structures seem to be related to the antiepileptic effects of lamotrigine or vigabatrin on complex partial seizures. The thalamus is essential in the oscillating electrical activity associated with spike and wave discharges in the generalized epilepsies. Valproate reduced regional cerebral glucose metabolism in the thalamus in healthy volunteers and seemed to have a greater effect on subcortical thalamic cerebral glucose metabolism. These findings and our result of decreased glucose metabolism in the thalamus may be related to the antiepileptic effects of valproate and lamotrigine on generalized seizures. Moreover, centromedian nuclei of the thalamus, which showed hypometabo-
Table. Brain Regions Showing Decreased Glucose Metabolism After Lamotrigine Administration*  

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Side</th>
<th>Talairach Coordinate, mm†</th>
<th></th>
<th>P Value</th>
<th></th>
<th>Uncorrected</th>
<th></th>
<th>FDR Corrected</th>
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<tr>
<td>Thalamus (centromedian nucleus)</td>
<td>L</td>
<td>14 -24 4</td>
<td>4</td>
<td>2.95</td>
<td>.004</td>
<td>.004</td>
<td>.003</td>
<td></td>
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<tr>
<td></td>
<td>R</td>
<td>-6 -22 2</td>
<td>2</td>
<td>2.96</td>
<td>.004</td>
<td>.004</td>
<td>.003</td>
<td></td>
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<tr>
<td>Caudate nucleus</td>
<td>L</td>
<td>-6 14 8</td>
<td>8</td>
<td>3.11</td>
<td>.003</td>
<td>.003</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>18 7 21</td>
<td>21</td>
<td>3.84</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td></td>
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<tr>
<td>Putamen, lentiform nucleus</td>
<td>L</td>
<td>-28 -15 -1</td>
<td>-1</td>
<td>4.00</td>
<td>.&lt;.001</td>
<td>.001</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>-6 7 -9</td>
<td>-9</td>
<td>4.09</td>
<td>.&lt;.001</td>
<td>.001</td>
<td>.001</td>
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<tr>
<td>Superior frontal gyrus</td>
<td>L</td>
<td>-6 26 52</td>
<td>52</td>
<td>3.40</td>
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<td>.001</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>14 28 52</td>
<td>52</td>
<td>3.25</td>
<td>.002</td>
<td>.002</td>
<td>.002</td>
<td></td>
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<tr>
<td>Middle frontal gyrus</td>
<td>L</td>
<td>-42 -22 52</td>
<td>52</td>
<td>3.66</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>10 -27 66</td>
<td>66</td>
<td>3.54</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td></td>
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<tr>
<td>Precentral gyrus</td>
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<td>-16 -11 -26</td>
<td>-26</td>
<td>4.13</td>
<td>.&lt;.001</td>
<td>.001</td>
<td>.001</td>
<td></td>
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<tr>
<td></td>
<td>R</td>
<td>44 -8 -43</td>
<td>-43</td>
<td>3.73</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td></td>
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<tr>
<td>Entorhinal gyrus</td>
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<td>-32 23 -29</td>
<td>-29</td>
<td>3.77</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
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<tr>
<td></td>
<td>R</td>
<td>24 -16 -26</td>
<td>-26</td>
<td>3.78</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
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<tr>
<td>Pericalcine gyrus</td>
<td>L</td>
<td>-8 45 66</td>
<td>66</td>
<td>4.04</td>
<td>.&lt;.001</td>
<td>.002</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>46 -44 56</td>
<td>56</td>
<td>3.15</td>
<td>.002</td>
<td>.002</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>L</td>
<td>-4 -18 -16</td>
<td>-16</td>
<td>3.80</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>4 -18 -16</td>
<td>-16</td>
<td>3.20</td>
<td>.002</td>
<td>.002</td>
<td>.002</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FDR, false discovery rate; L, left; R, right.

*Height threshold, corrected P<.05; extent threshold k > 125.
†Coordinates are defined in the stereotactic space of Talairach (Research Imaging Center, The University of Texas Health Science Center at San Antonio). x represents the lateral distance from the midline (positive, right); y, the anteroposterior distance from the anterior commissure (positive, anterior); and z, the rostrocaudal distance from the bicommissural plane (positive, rostral).

Figure. The brain regions showing decreased glucose metabolism after lamotrigine administration in patients with idiopathic generalized epilepsy. A, Cerebral metabolism decreased in bilateral thalami, the striatum, bilateral superior frontal gyri, the left middle frontal gyrus, left pericentral gyri, the right superior parietal lobule, the left entorhinal area, bilateral parahippocampal gyri, and the right inferior temporal gyrus as a T1 template overlaid magnetic resonance imaging after lamotrigine administration (at false discovery rate [FDR]-corrected P<.05). The order of left to right panels is arranged in the anterior to posterior direction in coronal images of the brain. B, Cerebral metabolism decreased in the left rectosubcallosal gyrus in a sagittal image (at FDR-corrected P<.05). C, Cerebral metabolism decreased in bilateral substantia nigra and bilateral basal temporal regions in axial images (at FDR-corrected P<.05). The order of left to right panels is arranged in the superior to inferior direction in axial images of the brain. The left side of the images represents the left side of the brain. A indicates anterior; L, left; P, posterior; and R, right.

lamotrigine administration, are closely interconnected with the striatum. Thus, the hypometabolism observed in bilateral thalami, striatum, substantia nigra, and cortical areas after the administration of lamotrigine suggests that lamotrigine may reduce excitability in pathologically overactive corticobasal ganglia-
entorhinal areas and the thalamocortical network in cases of
generalized epilepsy, thereby inducing an antiepileptic
effect. In depressed patients, smaller rectal or sub-
genual gyri volumes are commonly reported, implicating
orbitofrontal cortex dysfunction. Lamotrigine has
been suggested to be effective for treating bipolar depres-
sion by attenuation of the supranormal neuronal ac-
tivities. Thus, decreased metabolism in the orbito-
frontal cortex after lamotrigine administration may explain
the mechanism underlying the effect of lamotrigine in
patients with a mood disorder. There are some limita-
tions in this study: (1) absolute quantification of cere-
bral metabolism was not performed and (2) the absence of
neuropsychological data before and after lamotrigine
treatment put a limitation on the further description of
cognitive performance and the metabolic changes in cer-
tain brain regions.

To avoid the focal metabolism changes associated with
partial epilepsy and other AEDs, we recruited a set of drug-
naive patients with IGE, in whom brain MRI had re-
vealed no lesions.

In conclusion, lamotrigine treatment reduced glu-
cose metabolism in multiple regions of the cerebral cor-
tex, basal ganglia, and thalamus in the patients with IGE.
To our knowledge, this study is the first to investigate
the regional effects of lamotrigine on cerebral glucose me-
tabolism in drug-naive patients with IGE.

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