Topiramate increases the risk of valproic acid–induced encephalopathy

*Young Noh, †Dong Wook Kim, ‡Kon Chu, §Soon-Tae Lee, ¶Keun-Hwa Jung, ¶Hye-Jin Moon, and ¶Sang Kun Lee

*Department of Neurology, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea; †Department of Neurology, Konkuk University College of Medicine, Seoul, Korea; and ‡Comprehensive Epilepsy Center, Department of Neurology, Seoul National University Hospital, Seoul, Korea

Summary
Metabolic encephalopathy is a rare but serious complication of valproic acid (VPA) therapy that usually presents with impaired consciousness or increased seizure frequency. Although it has been suggested that topiramate (TPM) increases the risk of VPA-induced encephalopathy, the additional risk in patients receiving TPM therapy has not been evaluated. We reviewed all adult patients who took VPA between January 2005 and February 2009 at the Seoul National University Hospital and identified patients with VPA-induced encephalopathy based on clinical and electroencephalography (EEG) data. Information on sex, age, serum ammonia level, serum VPA level, liver function test, and EEG was collected from patient registry and medical data. We enrolled 8,372 patients who received VPA therapy and 1,236 patients who received VPA/TPM combination therapy. We identified 11 patients with VPA-induced encephalopathy (0.13%), 7 of whom received a combination therapy of VPA and TPM. The odds ratio of VPA-induced encephalopathy with TPM over that without TPM was 10.16. There were no significant differences in sex distribution, number of antiepileptic agents, ammonia level, VPA serum level, underlying diseases, dosage of VPA, duration of VPA treatment, treatment of encephalopathy, and outcomes between the two groups. Our study showed that the prevalence of VPA-induced encephalopathy is approximately 0.1% among patients treated with VPA and that the risk of this condition, although still low, can increase by approximately 10 times in the presence of TPM therapy. Based on these results, we suggest that TPM should be carefully used in patients receiving VPA treatment.

Key Words: Valproic acid, Topiramate, Adverse effects, Incidence.

Methods
We included 8,372 adult patients (age ≥16 years) to whom VPA was prescribed, including 1,236 patients who received both VPA and TPM treatments between January 2005 and February 2009 at the Seoul National University Hospital. Demographic findings are presented in Table 1. We identified patients with VPA-induced encephalopathy based on clinical signs, that is, stuporous encephalopathy and electroencephalography (EEG) findings in relation to VPA. We excluded patients with other potential causes of encephalopathy such as underlying hepatic or renal diseases and administration of several antibiotics including cefepime and imipenem. Information on sex, age, type of epilepsy, dosage and duration of VPA treatment and of other coadministered AEDs, serum ammonia level, serum VPA level, liver function test, EEG, clinical presentations, management of the patients, and outcomes was collected from patient registries and medical data.

For statistical analysis, SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, U.S.A.) was used for statistical analyses.
We identified 11 patients with VPA-induced encephalopathy (0.13%): 7 received a combination therapy of VPA and TPM (0.57%) and 4 were administered VPA without TPM (0.056%) (p < 0.001, Fisher’s exact test). Basic demographics of the study population and demographic and major laboratory characteristics of the patients with encephalopathy are presented in Table 1. All of the patients with encephalopathy had epilepsy and were taking more than one AED. The clinical presentations observed were sleeping tendency and confusion in nearly all patients when the regimen of VPA or TPM was changed. Among the patients with VPA without TPM, drug changes considered responsible were addition of VPA (n = 1), increase of VPA and addition of TPM with short intervals (n = 2), and coadministration of VPA and TPM and shortly after increase of VPA with intravenous injection (n = 1). Among the patients with VPA and TPM, drug changes considered responsible were addition of TPM to VPA (n = 1), coadministration of VPA and TPM, drug changes considered responsible were addition of VPA (n = 2), increase of VPA with intravenous injection (n = 1), and initial administration of VPA (n = 1). Median time interval between the drug change and the onset of clinical signs of encephalopathy was 18 days (interquartile range, 5–395 days) in all patients with encephalopathy. Each time interval was 25 days (8–450 days) in the patients with VPA and TPM and 6 days (2–298 days) in the patients with VPA without TPM, with the difference not significant using Mann-Whitney U-test. All patients recovered after withdrawal of VPA. Lactulose was used concomitantly with the discontinuation of VPA in eight patients and L-carnitine was administered to two patients (Table 2).

The odds ratio of VPA-induced encephalopathy with TPM over VPA-induced encephalopathy without TPM was 10.16 (p < 0.001, 95% confidence interval [95% CI] 3.0–34.7). There were no statistically significant differences in sex distribution, number of antiepileptic agents, ammonia level, VPA serum level, dosage of VPA, duration of VPA treatment, treatment of encephalopathy, and outcomes between the two groups.

**DISCUSSION**

VPA-induced encephalopathy is a serious complication that can be fatal; however, it is reversed by the discontinuation of VPA. Therefore, its early detection is important. VPA-induced encephalopathy is more common when VPA is used in combination with other AEDs, such as TPM, phenobarbital, phenytoin, carbamazepine, or lamotrigine (Warter et al., 1983; Hamer et al., 2000; Fan et al., 2008; Gomez-Ibanez et al., 2011). Several anecdotal reports have provided evidence that suggests that TPM increases the risk of VPA-induced encephalopathy (Longin et al., 2002; Latour et al., 2004; Cheung et al., 2005; Deutsch et al., 2009). However, the additional risk of VPA-induced encephalopathy in the presence of concomitant TPM has not been evaluated.

In our study, the incidence of VPA-induced encephalopathy was 0.13%, which increased to 0.57% in the presence of TPM. The additional risk of VPA-induced encephalopathy with TPM over its risk without TPM was estimated as being 10.16. Although there was no significant difference in clinical features between the two groups, the median age was significantly different: the median age of patients treated with VPA and TPM was 42.1 years, whereas that of patients treated with VPA without TPM was 66 years. This discrepancy can be in part explained by the nature of the population studied; the mean age of the patients treated with VPA and TPM was 42.1 years, whereas that of the patients treated with VPA without TPM was 66 years. It can be associated with the fact that clinicians have a tendency to hesitate to prescribe TPM to elderly patients because cognitive impairment is a well-known side effect of the drug. On the other hand, given that elderly patients are supposed to have used AED for a long time, they are likely to continue to use old-generation AEDs compared with newer drugs, such as TPM.

The median interval between the drug changes responsible for encephalopathy and the onset of clinical signs was 18 days (interquartile range, 5–395 days). However, delayed encephalopathy developed in three patients...
<table>
<thead>
<tr>
<th>Age (years)/sex</th>
<th>Type of epilepsy</th>
<th>Clinical signs</th>
<th>Time interval between drug change and onset of clinical signs</th>
<th>Dosage of VPA (mg/day)</th>
<th>Additional AEDs at diagnosis of encephalopathy</th>
<th>Laboratory results at diagnosis</th>
<th>EEG</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>66/F</td>
<td>Localization-related epilepsy</td>
<td>Sleeping tendency, apathy, abulia, urinary incontinence</td>
<td>3 years after TPM addition</td>
<td>900</td>
<td>TPM, CBZ, VGB</td>
<td>Ammonia: 173 VPA level: 91 OT/PT: 11/3</td>
<td>Several sharp waves on bilateral frontal area, intermittent triphasic waves</td>
<td>Recovery after VPA withdrawal and lactulose enema</td>
</tr>
<tr>
<td>25/M</td>
<td>Localization-related epilepsy</td>
<td>Sleeping tendency, confusion</td>
<td>25 days after VPA increase, 24 days after TPM addition</td>
<td>2,700</td>
<td>TPM, PB, LEV, PHT</td>
<td>Ammonia: 154 VPA level: 64 OT/PT: 42/36</td>
<td>Continuous δ activity, generalized</td>
<td>Recovery after VPA withdrawal and lactulose enema</td>
</tr>
<tr>
<td>58/M</td>
<td>Localization-related epilepsy</td>
<td>Sleeping tendency, confusion, upward eyelid deviation, nausea, vomiting</td>
<td>8 days after VPA increase</td>
<td>2,000</td>
<td>OCB, LTG, PGB</td>
<td>Ammonia: 173 VPA level: 73 OT/PT: 18/8</td>
<td>Background slowing, semirhythmic δ activities in Rt. centroparietal area</td>
<td>Recovery after VPA withdrawal, lactulose enema, and L-carnitine administration (50 mg/kg/day)</td>
</tr>
<tr>
<td>22/F</td>
<td>Localization-related epilepsy</td>
<td>Sleeping tendency, confusion, upward eyelid deviation</td>
<td>27 days after TPM addition</td>
<td>1,200</td>
<td>TPM, PHT, LTG, LEV</td>
<td>Ammonia: 259 VPA level: 58 OT/PT: 35/22</td>
<td>Continuous rhythmic δ to δ waves</td>
<td>Recovery after VPA withdrawal and lactulose enema</td>
</tr>
<tr>
<td>43/M</td>
<td>Localization-related epilepsy</td>
<td>Sleeping tendency, confusion</td>
<td>18 days since VPA increase, 3 days after TPM addition</td>
<td>2,000</td>
<td>TPM, LEV</td>
<td>Ammonia: 83 VPA level: &gt;150 OT/PT: 23/23</td>
<td>Intermittent rhythmic δ waves in Rt. frontocentral area</td>
<td>Recovery after VPA withdrawal and lactulose enema</td>
</tr>
<tr>
<td>65/F</td>
<td>Localization-related epilepsy</td>
<td>Sleeping tendency, intermittent limb myoclonus</td>
<td>2 days after VPA increase and formula change</td>
<td>1,200 (p.o.) → 1,800 (IV)</td>
<td>PHT, CBZ</td>
<td>Ammonia: 124 VPA level: 140 OT/PT: 17/9</td>
<td>Background slowing, a few sharp and slow waves in bilateral frontotemporal areas</td>
<td>Recovery after VPA withdrawal and lactulose enema</td>
</tr>
<tr>
<td>68/F</td>
<td>Generalized epilepsy</td>
<td>Sleeping tendency, slow ideation, slow motor activity</td>
<td>3 days after VPA increase</td>
<td>1,440</td>
<td>CBZ</td>
<td>Ammonia: 105 VPA level: 62 OT/PT: 14/8</td>
<td>Background slowing, triphasic waves</td>
<td>Recovery after VPA withdrawal</td>
</tr>
<tr>
<td>51/F</td>
<td>Localization-related epilepsy</td>
<td>Confusion, fine hand tremor, nausea, slurred speech</td>
<td>15 months after TPM addition</td>
<td>1,200 (p.o.)</td>
<td>TPM, CBZ, PB</td>
<td>Ammonia: 238 VPA level: 65 OT/PT: 14/13</td>
<td>Background slowing, triphasic waves</td>
<td>Recovery after VPA withdrawal and lactulose enema</td>
</tr>
<tr>
<td>35/F</td>
<td>Localization-related epilepsy</td>
<td>Sleeping tendency, confusion</td>
<td>5 days after VPA addition</td>
<td>1,000</td>
<td>TPM, CBZ</td>
<td>Ammonia: 287 VPA level: 51 OT/PT: 12/1</td>
<td>Frequent triphasic waves</td>
<td>Recovery after VPA withdrawal, lactulose enema, and L-carnitine administration</td>
</tr>
<tr>
<td>53/F</td>
<td>Localization-related epilepsy</td>
<td>Sleeping tendency, confusion, nausea, vomiting</td>
<td>8 days after VPA and TPM coadministration, 2 days after VPA increase and formula change</td>
<td>300 (p.o.) → 900 (IV)</td>
<td>TPM</td>
<td>Ammonia: 160 VPA level: 78 OT/PT: 16/12</td>
<td>Background slowing, continuous δ waves in Rt. posttemporal areas</td>
<td>Recovery after VPA withdrawal and lactulose enema</td>
</tr>
<tr>
<td>73/M</td>
<td>Unclassified epilepsy</td>
<td>Sleeping tendency</td>
<td>13 months after initial administration of VPA</td>
<td>1,750</td>
<td>LEV</td>
<td>Ammonia: 99 VPA level: 73 OT/PT: 49/24</td>
<td>Background slowing</td>
<td>Recovery after VPA withdrawal</td>
</tr>
</tbody>
</table>

VPA, valproic acid; TPM, topiramate; CBZ, carbamazepine; VGB, vigabatrin; PB, phenobarbital; LEV, levetiracetam; PHT, phenytoin; OXC, oxcarbazepine; LTG, lamotrigine; PGB, pregabalin; OT, SGOT, (serum glutamic oxaloacetic transaminase); PT, SGPT (serum glutamic pyruvate transaminase); p.o., per os; IV, intravenous.

*Units of the laboratory results, μmol for ammonia (11–55); μg/ml for VPA level; IU/L for OT (10–40); IU/L for PT (10–40).
(3 years in patient 1; 15 months in patient 8; 13 months in patient 11). VPA-induced encephalopathy with variable time interval including several months to years was reported previously (Dealberto, 2007). We presumed the causes were related to one of the cumulative mechanism of the encephalopathy; however, exact mechanism or provoking factors remained to be elucidated. In addition, the time intervals in the two groups tended to be different, although statistically significant difference was not shown. Therefore, it seems that the period to be cautious about the VPA-induced encephalopathy might be different.

Nine of 11 patients with encephalopathy had permanent intracranial lesions. Previous studies reported that VPA-induced encephalopathy occurred more frequently in patients with intracranial lesions (Hamer et al., 2000; Gerstner et al., 2006; Gomceli et al., 2007). The causes are presumed that epilepsies in patients with intracranial lesions have a tendency to be controlled poorly, so high-dosage treatment or polytherapy is more needed. Alternatively, damage to the blood–brain barrier at the intracranial lesions may explain these findings, because changes in blood–brain barrier permeability may facilitate the development of encephalopathy induced by hyperammonemia (Wang & Saab, 2003).

We acknowledge that this study had some drawbacks. First, because the study was based on a retrospective design through chart review, the cases that were not suspected or not charted by doctors could be missed. Therefore, it is possible that the incidence of VPA-induced encephalopathy was underestimated. Secondly, we investigated only severe encephalopathy that needed management through admission. As a result, mild forms that might show subtle symptoms and recovered soon without management, if any, may have been excluded. Consequently, the incidence of VPA-induced encephalopathy estimated in this study concerned severe encephalopathy.

However, to the best of our knowledge, this was the first study to estimate the additional risk of VPA-induced encephalopathy in the presence of coadministration of VPA and TPM. Although VPA-induced encephalopathy remains a rare complication of treatment, the risk of this condition may increase by approximately 10 times in the presence of TPM therapy. Our results suggest that TPM should be used carefully in patients receiving VPA therapy.

Acknowledgments
This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A101535). S.K.L. was supported by Seoul National University Hospital (0320101160).

Disclosure
The authors report no disclosures. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References


