Risk Factors of Hyperammonemia in Patients With Epilepsy Under Valproic Acid Therapy

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INTRODUCTION

Valproic acid (VPA) is an antiepileptic drug (AED) that is widely used in the treatment of epilepsy, migraine, and psychiatric disorders. The most commonly reported adverse events associated with VPA include fatigue, gastrointestinal disturbances, weight gain, tremor, hair loss, thrombocytopenia, an increase in hepatic enzymes, and teratogenicity. Hyperammonemia has been reported in patients who receive VPA therapy. Although most patients are asymptomatic and the clinical significance of hyperammonemia associated with VPA therapy is still under debate, it may also rarely lead to hyperammonemic encephalopathy, which is associated with significant morbidity and central nervous system (CNS) damage.

Ammonia is a product of the catabolism of proteins that contain nitrogen. It is normally converted to urea in the liver hepatocytes rendering it nontoxic, and it is then eliminated via the kidneys. Under normal conditions, the concentration of ammonia in the circulation remains low, typically less than 50 μmol/L (85 μg/dL). Studies have shown that a variety of environmental factors and medications may elevate blood ammonia levels leading to toxic effects on the CNS. The exact mechanism of VPA-induced hyperammonemia is still unknown. The possible mechanisms might be related to an imbalance between ammoniagenesis and ammonia disposal in the urea cycle that includes direct inhibition of the mitochondrial urea cycle enzyme, carbamoyl phosphatase synthetase (CPS) I by VPA or its metabolites, an indirect effect on CPS I through interference in the synthesis of N-acetylglutamate, and inhibition of the mitochondrial fatty acid beta-oxidation pathway.

The reported prevalence of hyperammonemia in patients receiving VPA therapy is highly variable, ranging from 2% to 80%. However, only a few studies have reported the possible risk factors associated with VPA-induced hyperammonemia. Two large-scale studies in Japan conducted on adult and pediatric patient groups reported the risk factors for hyperammonemia associated with VPA therapy, including VPA dose, female gender, and the concomitant use of phenytoin, phenobarbital, or topiramate. Although hyperammonemia induced by VPA therapy is mostly asymptomatic, it may be an unrecognized adverse effect in patients with epilepsy on VPA therapy. In this article, we analyzed the risk factors for hyperammonemia in patients with epilepsy who received VPA treatment for seizure control.

PATIENTS AND METHODS

Subjects

This was a single-center, prospective, observational study. From June 2012 to May 2013, 158 patients aged older...
TABLE 1. Demographic Data of the 158 Patients Receiving Valproic Acid Therapy

| Characteristics                  | Values               |
|----------------------------------|----------------------|
| Age (y)¹                         | 38 (18–88)           |
| Gender: female/male; N/N (%)      | 54/104 (34.2% vs 65.8%) |
| Body mass index (kg/m²)²          | 24.1 (15.8–43.9)     |
| Age at onset (y)²                 | 18 (1–87)            |
| Duration of epilepsy (y)²         | 14 (4.5, 24)         |
| Seizure type; N (%)               |                     |
| Partial                          | 114 (72.2%)          |
| Generalized                      | 44 (27.8%)           |
| Etiology; N (%)                  |                     |
| Idiopathic/cryptogenic           | 62 (39.2%)           |
| Symptomatic                      | 96 (60.8%)           |
| Seizure control; N (%)            |                     |
| Seizure free                     | 54 (34.8%)           |
| Noneizure free                   | 103 (65.2%)          |
| Mode of AED therapy; N (%)        |                     |
| VPA monotherapy                  | 31 (19.6%)           |
| VPA combination therapy          | 127 (80.4%)          |
| Dose of VPA use (mg/day)³         | 1000 (787, 1500)     |
| Blood VPA level (μg/mL)³          | 58.49 (37.69, 77.35) |
| Duration of VPA therapy (y)³      | 8 (3, 12)            |
| Plasma level of ammonia (μg/dL)⁴ | 75.5 (56.75, 100.00) |
| Dose of combined AED (mg/day)²    | 120 (90, 150)        |
| Phenobarbital                     | 300 (300, 300)       |
| Carbamazepine                     | 800 (750, 1000)      |
| Topiramate                        | 200 (162, 375)       |
| Oxcarbazepine                     | 1200 (600, 1200)     |
| Lamotrigine                       | 200 (200, 300)       |
| Levetiracetam                     | 1500 (1000, 2000)    |
| Comorbidity; N (%)                |                     |
| Diabetes mellitus                 | 12 (7.6%)            |
| Hypertension                      | 27 (17.1%)           |
| Cerebrovascular disease           | 20 (12.7%)           |
| Brain tumor                       | 17 (10.8%)           |
| Psychiatric disorder              | 14 (8.9%)            |
| Hepatitis B                       | 13 (8.2%)            |
| Hepatitis C                       | 7 (4.4%)             |

AED = antiepileptic drug, IQR = interquartile range (25th percentile, 75th percentile), VPA = valproic acid.

Values are expressed as ¹median (range) or ²median (IQR).

was defined as no seizure attacks for at least 12 months under current antiepileptic medication according to the consensus proposal of the International League Against Epilepsy. Liver enzyme inducers of AEDs included phenobarbital, phenytoin, and carbamazepine. Weak liver enzyme inducers included oxcarbazepine and topiramate. Levetiracetam and lamotrigine were classified as nonenzyme inducers.

Assessment of Blood Ammonia Level

Blood samples were taken during the interictal state. As transient hyperammonemia has been reported to be associated with seizures, the blood samples collected from the patients with a recent seizure event were excluded from this study. In our clinical practice, blood samples are collected into a heparinized tube that is then immediately placed in ice water. Blood samples were centrifuged at 3000rpm for 10 minutes to obtain serum samples. The plasma ammonia and VPA levels were rapidly analyzed by the central laboratory of Chang Gung Memorial Hospital. In brief, the level of ammonia was measured by a timed endpoint method using an ammonia reagent kit (Bechman Coulter, Brea, CA). The changes in the absorbance at 340 nm were monitored by a UniCel DxC 800i system (Bechman Coulter) to calculate the concentration of ammonia. A fluorescence polarization immunoassay was used to measure the level of VPA in conjunction with an AxSYM analyzer (Abbott Laboratories, Abbott Park, IL). The blood samples were sent to the central laboratory for the analysis of complete blood cell count and serum levels of creatinine, alanine aminotransferase, alkaline phosphatase, and gamma glutamyl transpeptidase (γGT). The cut-off value of the reference level of ammonia is 93 μg/dL. Therefore, we defined hyperammonemia as patients whose blood ammonia level was higher than 93 μg/dL.

Statistical Analyses

For categorical variables, the chi-square test or Fisher’s exact test was used as appropriate. Fisher’s exact test was used when 1 cell had an expected count of less than 5. Continuous variables such as age, age at onset, duration of epilepsy, body height, weight, body mass index, VPA dose, plasma VPA level, and biochemistry results were compared using the Mann–Whitney U test. Pearson correlations were performed to test the association between continuous variables, including the plasma level of VPA and ammonia. Logistic regression analysis was used to test the independent association between each risk variable as a predictor of hyperammonemia. Variables in the regression model included gender, dose of daily VPA, and combined medications including liver enzyme-inducing AEDs and antipsychotic drugs. The VPA dose and γGT between those taking and not taking liver enzyme inducers were compared by the Mann–Whitney test. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, version 11.0 for Windows; Chicago, IL). A P value of <0.05 was considered to be statistically significant.

RESULTS

In total, 158 patients (54 females and 104 males) were enrolled in this study. The demographic data of the patients are listed in Table 1. The median age was 38 years (range: 18–88 y). Sixty-two (39.2%) patients suffered from idiopathic or cryptogenic epilepsy, whereas the remaining patients...
(60.8%) suffered from symptomatic etiologies including cerebrovascular accidents (N = 20), perinatal brain damage (N = 9), central nervous systemic infections (N = 11), head trauma (N = 36), neoplasms (N = 17), and immune diseases (N = 3). Of the 158 patients, 55 (35%) were seizure free and 103 patients were not seizure free in the past 1 year. The dosage of VPA used ranged from 300 to 2250 mg/day, and the blood level of VPA ranged from 3.21 μg/mL to 113.27 μg/mL. The level of ammonia ranged from 27 to 319 μg/dL. Thirty-one patients (19.6%) received VPA monotherapy and the other 127 patients (80.4%) received combination therapy with other AEDs. The frequency of hyperammonemia (ammonia level >93 μg/dL) associated with VPA therapy was estimated at 27.8% (N = 44) in all patients, 6.4% (2/31) in VPA monotherapy patients and 33.1% (42/127) in patients with combination therapy. The symptoms of VPA-induced hyperammonemia included nausea (N = 2), fatigue (N = 2), ataxia (N = 1), and consciousness disturbance (N = 1). One patient had encephalopathy with consciousness disturbance with an ammonia level of 319 μg/dL. None of the patients had seizure aggravation during the period when they had a higher ammonia level. The VPA dosage was reduced in 6 patients, and 3 patients gradually discontinued VPA treatment because of the adverse effects or the patient’s or family’s request. The level of ammonia returned to normal in all patients who reduced or discontinued VPA therapy.

**Risk Factors of Hyperammonemia in the Patients With VPA Therapy**

Comparisons of the clinical features between the patients with or without hyperammonemia are listed in Table 2. Statistical analysis between the 2 patient groups revealed that male gender, the dose of VPA, combination therapy, concomitant use with liver enzyme-inducing AEDs or antipsychotic drugs, comorbidity with brain tumor, and elevated serum γGT were significantly associated with VPA-induced hyperammonemia. After analyzing these variables, male gender (P < 0.001, odds ratio [OR] = 8.456, 95% confidence interval [CI] = 2.565–27.874), the dose of VPA (P = 0.029, OR = 1.001, 95% CI = 1.000–1.002), and combination therapy with liver enzyme-inducing AEDs (P = 0.014, OR = 2.834, 95% CI = 1.232–6.516) and antipsychotic drugs (P = 0.011, OR = 6.971, 95% CI = 1.559–31.160) were independently associated with hyperammonemia. There were no significant associations with the other variables including age, body mass index, semiology of epilepsy, duration of VPA therapy, etiology, associated medical diseases, and concomitant use of other medical medications (except for antipsychotic drugs). Among 10 patients who received combination therapy with antipsychotic drugs, 7 (70%) had hyperammonemia. The antipsychotic drugs included aripiprazole, sulpride, amisulpride, risperidone, paliperidone, and quetiapine.

Based on Pearson correlation analysis, the plasma ammonia level showed a linear correlation with the blood concentration of VPA (r = 0.21, P = 0.008) (Figure 1). An increase of 1 mg in the dosage of VPA increased the risk of hyperammonemia by 0.1%.

**Relationship of Combination Therapy With Enzyme-Inducing AEDs in VPA-Induced Hyperammonemia**

The regimens of combined AEDs are listed in Table 2. Levetiracetam (N = 77) was most frequently used in combination therapy, followed by lamotrigine (N = 33), carbamazepine (N = 26), phenytoin (N = 21), topiramate (N = 20), phenobarbital (N = 19), and oxcarbazepine (N = 15). Among the 58 patients who received combination therapy with liver enzyme-inducing AEDs, 25 had hyperammonemia. However, the patients undergoing combination therapy with the weak enzyme inducers (topiramate and oxcarbazepine) or nonenzyme inducers (levetiracetam and lamotrigine) did not show significantly increased plasma levels of ammonia. Table 3 shows the contribution of 3 liver enzyme-inducing AEDs (carbamazepine, phenytoin, and phenobarbital) in VPA-induced hyperammonemia. The results showed that the patients receiving combination therapy with phenytoin, carbamazepine, or phenobarbital had a higher percentage of hyperammonemia. In addition, the patients who received combination therapy with liver enzyme-inducing AEDs had significantly increased plasma ammonia levels compared with the patients who received...
| Age (y) | Normal Ammonia (N = 114) | Hyperammonemia (N = 44) | P Value |
|---------|--------------------------|-------------------------|---------|
| 38.5 (18–88) | 35.5 (24–76) | 0.737 |
| Gender; N | | | |
| Female | 49 | 5 | <0.001* |
| Male | 65 | 39 | |
| Body mass index (kg/m²) | 24.1 (16.2–34.1) | 24.1 (15.8–43.9) | 0.613 |
| Age at onset (y) | 18 (12, 34) | 17.5 (9.2, 36.7) | 0.454 |
| Duration of epilepsy (y) | 13 (4, 25) | 20 (8, 24) | 0.254 |
| Seizure type; N | | | |
| Partial | 83 | 32 | 0.992 |
| Generalized | 31 | 12 | |
| Etiology; N | | | |
| Idiopathic/cryptogenic | 44 | 18 | |
| Symptomatic | 70 | 26 | 0.790 |
| Seizure control; N | | | |
| Seizure free | 36 | 19 | |
| Nonseizure free | 78 | 25 | 0.170 |
| Dose of VPA use (mg/day) | 1000 (750, 1500) | 1250 (1000, 1500) | 0.009*** |
| Duration of VPA therapy (y) | 7 (3, 12) | 9 (3, 12) | 0.629 |
| Blood VPA level (µg/mL) | 56.03 (35.21, 76.19) | 67.98 (46.82, 80.66) | 0.060 |
| Mode of AED therapy; N | | | |
| VPA monotherapy | 29 | 2 | 0.003* |
| Combination therapy | 85 | 42 | |
| Combined AED; N | | | |
| Liver enzyme inducer | 33 | 25 | 0.001** |
| Phenobarbital | 9 | 10 | 0.010** |
| Phenytoin | 11 | 10 | 0.030 |
| Carbamazepine | 16 | 10 | 0.472 |
| Weakly liver enzyme inducer | 16 | 9 | 0.322 |
| Topiramate | 12 | 8 | 0.195 |
| Oxcarbazepine | 10 | 5 | 0.762 |
| Nonenzyme inducer | 36 | 9 | 0.165 |
| Lamotrigine | 24 | 9 | 0.934 |
| Levetiracetam | 53 | 24 | 0.297 |
| Concomitant medications; N | | | |
| Antidepressant | 4 | 3 | 0.399 |
| Antipsychotic drug | 3 | 7 | 0.005* |
| Lipid lowering agent | 7 | 1 | 0.445 |
| Antihypertensive drug | 20 | 5 | 0.467 |
| Oral hypoglycemic agent | 6 | 2 | 1.000 |
| Comorbidity; N | | | |
| Diabetes mellitus | 10 | 2 | 0.511 |
| Hypertension | 20 | 7 | 0.772 |
| Cerebrovascular disease | 16 | 4 | 0.594 |
| Brain tumor | 16 | 1 | 0.042** |
| Psychiatric disorder | 7 | 7 | 0.053 |
| Hepatitis B | 10 | 3 | 1.000 |
| Hepatitis C | 5 | 2 | 1.000 |
| Laboratory data | | | |
| Platelet (10³/µL) | 203 (173, 254) | 189 (166, 239) | 0.389 |
| Serum creatinine (mg/dL) | 0.80 (0.62, 0.93) | 0.78 (0.67, 0.92) | 0.929 |
| ALT (U/L) | 16.5 (11, 26) | 19 (13, 26) | 0.329 |
| ALK-P (U/L) | 62.5 (52, 74) | 65 (50, 82) | 0.378 |
| γGT (U/L) | 18 (9, 35) | 35 (5, 83) | <0.001*** |

AED = antiepileptic drug, ALK-P = alkaline phosphatase, ALT = alanine aminotransferase, γGT = gamma glutamyl transpeptidase; IQR = interquartile range (25th percentile, 75th percentile), VPA = valproic acid.

Values are expressed as median (range) or median (IQR).

*P < 0.05 by Fisher’s exact test; **P < 0.05 by the chi-square test; ***P < 0.01 by the Mann–Whitney test.
VPA monotherapy. However, there were no significant differences between these 3 patient groups with enzyme-inducing combination therapy.

**DISCUSSION**

In the present study, we confirmed that hyperammonemia is often an asymptomatic adverse effect in patients with epilepsy receiving VPA therapy. Furthermore, we demonstrated the novel observation that the blood level of ammonia was significantly correlated with the dosage of VPA and the plasma concentration of VPA. An increase of 1 mg in the dosage of VPA increased the risk of hyperammonemia by 0.1%. In addition, combination treatment with liver enzyme-inducing AEDs and antipsychotic drugs increased the risk of hyperammonemia.

In this article, the patients who had hyperammonemia related to any etiology except for VPA therapy were excluded. Therefore, no patient had preexisting hyperammonemia before VPA therapy. In addition, the dose of VPA was not adjusted according to the blood ammonia level before treatment. In the patients with hyperammonemia, reduced or discontinued VPA led to the blood ammonia level returning to a normal range, indicating the causality of hyperammonemia with VPA therapy in patients with epilepsy.

The reported prevalence of hyperammonemia under VPA therapy is highly variable, ranging from 2% to 80%.\(^6,10\) In the current study, the frequency of hyperammonemia associated with VPA therapy was 27.8%. Among these patients, 5.1% had severe hyperammonemia (≥150 μg/dL). The incidence of hyperammonemia has been reported to be 0%–56% in patients receiving VPA monotherapy,\(^3, 6, 10, 12, 18, 19\) and 2%–80% in patients with combination therapy.\(^3, 6, 10, 12, 18, 19\) The high variability in incidence may be related to the different definitions of cut-off values for hyperammonemia in these studies. Furthermore, these studies were mostly conducted on pediatric patients. In the current study, hyperammonemia was found in 6.4% of the patients with VPA monotherapy and in 33.1% of the patients with combination therapy. Although a few studies\(^20, 22\) have reported that some patients with advanced hyperammonemia developed encephalopathy and status epilepticus, most of our patients with hyperammonemia were asymptomatic. Moreover, the patients with symptomatic hyperammonemia usually had a benign course and rapidly recovered after correction of blood ammonia with treatment such as lactulose therapy. In patients with severe and symptomatic hyperammonemia, it may be necessary to decrease the VPA dosage or to discontinue the drug completely.

Previous studies have identified diverse risk factors for VPA-induced hyperammonemia associated with VPA therapy, including age,\(^6, 10, 11\) and concomitant use of drugs such as phenytoin, phenobarbital, topiramate, and risperidone.\(^3, 6, 10, 23, 24\) Whether the degree of the decrease in blood ammonia level is related to the dosage of VPA is controversial. Emerging evidence has shown that the increase in ammonia concentration induced by VPA is dose dependent. Sharma et al\(^11\) reported that a higher incidence of hyperammonemia was noted in pediatric patients receiving a high dose of VPA (40–60 mg/kg/day) compared with those receiving a low dose (20–39 mg/kg/day). Recently, 2 large-scale studies\(^6, 10\) in Japan including 1 adult patient group and 1 pediatric patient group reported that the ammonia level was thought to be VPA dose dependent in both patient groups. In the present study, we also noted that hyperammonemia was significantly correlated with the dosage of VPA and the blood concentration of VPA.

The concomitant use of VPA with liver enzyme-inducing AEDs has been reported to be an important risk factor for VPA-induced hyperammonemia,\(^6, 10, 23\) particularly in combination with phenobarbital and phenytoin, and to a lesser extent with carbamazepine.\(^6\) The present study showed that the concomitant use of VPA with liver enzyme-inducing AEDs, including phenytoin, carbamazepine, and phenobarbital, also led to a higher incidence of hyperammonemia than VPA monotherapy. Among these 3 liver enzyme-inducing AEDs, phenobarbital had the strongest significant effect on VPA-induced hyperammonemia (\(P < 0.001\)), followed by phenytoin (\(P = 0.002\)), and carbamazepine (\(P = 0.007\)) compared with VPA monotherapy. However, the mechanisms involved in hyperammonemia with the concomitant use of VPA with liver enzyme-inducing AEDs remains unclear. Several mechanisms have been proposed. Liver enzyme-inducing AEDs may increase the activity of cytochrome P450 enzymes, resulting in a decrease in the blood level of VPA.\(^6, 10\) This interaction may lead physicians to increase the dose of VPA to maintain the therapeutic concentration, resulting in hyperammonemia.\(^6, 10\) We found that the patients with hyperammonemia under combination therapy with enzyme-inducing AEDs also received significantly higher doses of VPA (\(P = 0.002\)). Another possible mechanism is that enzyme-inducing AEDs may activate the cytochrome P450 enzymes in metabolic compounds such as propionate and 4-en-VPA, which inhibit CPS-1 activity and cause an increase in the blood ammonia level. Moreover, different genetic polymorphisms may also influence the effect of enzyme-inducing AEDs on VPA-induced hyperammonemia.\(^6\)

In the present study, the combination with newer generation AEDs including topiramate, oxcarbazepine, levetiracetam, and lamotrigine did not show significant effects on the increase in blood ammonia level. Topiramate is classified as a weak enzyme-inducing AED and carbonic anhydrase inhibitor.\(^16\) Combination therapy with topiramate and VPA has been reported to be associated with an increased risk of hyperammonemia.\(^23, 27, 28\) However, it was difficult to identify the risk of topiramate in VPA-induced hyperammonemia that may be because of the small number of patients in each group in this study, and further studies are needed to confirm this observation.

**TABLE 3. Comparison of VPA Monotherapy and VPA Combination Therapy With Liver Enzyme Inducers Between Patients With Normal Blood Ammonia Levels and Hyperammonemia**

| Comparison                  | Normal Ammonia | Hyperammonemia | \(P\) Value |
|-----------------------------|----------------|----------------|-------------|
| VPA monotherapy             | 29             | 2              |             |
| Phenobarbital with VPA      | 9              | 10             | 0.001*      |
| Carbamazepine with VPA      | 16             | 10             |             |
| Phenytoin with VPA          | 11             | 10             |             |

\(*\text{Person chi-square test.} \)
Concomitant use of VPA with antipsychotic drugs was also considered to be a risk factor for VPA-induced hyperammonemia in the presented study. VPA has been reported to have a drug interaction with risperidone, possibly through competition for protein-binding sites in the blood, and thus increases the risk of hyperammonemia.\textsuperscript{24,29,30} However, the number of patients receiving antipsychotic medications was small in this study. Further large-scale studies are necessary to analyze this risk factor.

Female gender has also been reported to be a risk factor for hyperammonemia.\textsuperscript{6,10} However, in the current study, the male patients had a higher frequency of hyperammonemia than the female patients. This may be partially related to the high percentage of male patients in the current study (66%) compared with the previous studies (45%–54%), and differences in diet between males and females.\textsuperscript{6,10}

Whether abnormal liver function is related to an increase of blood ammonia level in patients under VPA therapy is controversial.\textsuperscript{23,29} In the present study, coexisting chronic hepatitis or abnormal alanine aminotransferase and alkaline phosphatase levels were not significantly associated with VPA-induced hyperammonemia. However, we noted that the patients with hyperammonemia had significantly higher γGT levels. Based on the Mann–Whitney test results, we found that the level of γGT was significantly related to concomitant use of VPA with liver enzyme-inducing AEDs ($P<0.001$). While liver enzyme-inducing AEDs may increase the blood level of γGT,\textsuperscript{31,32} we, thus, suggest that an increased level of γGT may be related to the concomitant use of liver enzyme-inducing AEDs.

In conclusion, the use of VPA in adult patients with epilepsy was associated with a dose-dependent increase in blood ammonia levels. In addition, combination treatment with liver enzyme-inducing AEDs and antipsychotic drugs increased the risk of VPA-induced hyperammonemia. Although most of the patients with VPA-induced hyperammonemia were asymptomatic, some were symptomatic. If any patient taking VPA presents with symptoms such as nausea, fatigue, somnolence, ataxia, and consciousness disturbance, the blood ammonia level should be measured promptly, and if hyperammonemia is confirmed, the VPA dosage and concomitant use of enzyme-inducing AEDs should be decreased. In the patients who present with severe hepatic encephalopathy, it may be necessary to discontinue VPA altogether.

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