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Valproic acid–induced hyperammonemia: Incidence, clinical significance, and treatment management

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Abstract

Introduction: Valproic acid (VPA)–induced hyperammonemia poses several clinical challenges in psychiatric medicine. The reported incidence of this adverse effect varies widely across the literature. Furthermore, practitioners treat hyperammonemia in asymptomatic patients although studies suggest this practice is unnecessary. The purpose of this study is to evaluate if patients with VPA-induced hyperammonemia are appropriately identified for treatment based on their symptom presentation as well as determine the most efficacious treatment approach for VPA-induced hyperammonemia.

Methods: This study was completed at a community teaching hospital, and patients were retrospectively identified from June 1, 2011, to June 30, 2016, and included if they were admitted to a psychiatric unit, received at least 1 dose of VPA, and had at least 1 ammonia level drawn during admission. Hyperammonemia was defined as greater than 47 µmol/L, and symptomatic hyperammonemia was defined based on specific symptom presentation. The treatment modality was successful if the ammonia level was within normal range at discharge.

Results: Of the 357 patients screened, 347 patients met all inclusion criteria for analysis. The reported incidence of hyperammonemia was found to be 36% with 43.2% of those patients presenting with symptoms. Lactulose initiation was the most common treatment modality chosen (48.7%). Discontinuation of VPA was the most effective treatment (56.3% success rate).

Discussion: The results demonstrate that many patients with elevated ammonia levels are asymptomatic and therefore, based on findings within the literature, may not require treatment. Although lactulose was found to be the most common treatment initiated, the most effective was discontinuation of VPA.

Keywords: valproic acid, VPA, divalproex sodium, hyperammonemia, lactulose, levocarnitine, ammonia levels

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Introduction

Valproic acid (VPA)–induced hyperammonemia poses clinical challenges for providers. Elevated ammonia levels may occur after acute overdoses or with chronic use of VPA and do not necessarily cause encephalopathy. Most cases present asymptomatically with normal liver function tests.[1] The mechanism for VPA-induced hyperammonemia includes the urea cycle, the principal pathway for nitrogen metabolism; VPA treatment results in direct

inhibition of *N*-acetyl glutamate, leading to systemic disruption and increasing blood ammonia levels. This side effect can lead to VPA-induced hyperammonemic encephalopathy, which causes neurological slowing and electroencephalography changes; these changes can be reversible, but if untreated, may ultimately induce life-threatening coma.[2] Risk factors for VPA-induced hyperammonemia include concurrent topiramate use, urea cycle disorder, intellectual disability, and carnitine deficiency.[3] Furthermore, the range of normal ammonia levels is clinically debated. Some hospitals and experts cite acceptable levels as low as 30 μmol/L and as high as 60 μmol/L although symptoms may go undetected at higher levels.[4]

There are several different treatment options for VPA-induced hyperammonemia. The package label only mentions VPA discontinuation as follows: "Hyperammonemia and hyperammonemic encephalopathy: measure ammonia level if unexplained lethargy, vomiting, or changes in mental status, and also with concomitant topiramate use and consider discontinuation of VPA therapy."[5] The two most common medications used to treat VPA-induced hyperammonemia include lactulose and levocarnitine. Lactulose, a common treatment for hyperammonemic encephalopathy, enhances the diffusion of ammonia (NH_3) from the blood into the gut where conversion to ammonium (NH_4^+) occurs; this then produces an osmotic effect in the colon promoting removal from the body. Levocarnitine is also used for VPA-induced hyperammonemia; long term, high-dose VPA therapy can deplete carnitine stores, which has been associated with elevated ammonia levels. Levocarnitine therapy can counteract VPA-induced hyperammonemia by restoring carnitine reserves. Therefore, researchers have attempted to determine if levocarnitine may be better than lactulose for VPA-induced hyperammonemia specifically.[6,7]

Nakamura and colleagues[8] prospectively studied 22 psychiatric patients on VPA continuously for greater than 3 months with high plasma ammonia concentrations (>86 mcg/dL or 61 μmol/L). During the study period, levocarnitine was administered as fixed, oral, weight-based doses. Free carnitine, acylcarnitine, and total carnitine levels increased significantly. Additionally, there were statistically insignificant improvements in serum ammonia levels, VPA levels, and Brief Psychiatric Rating Scale scores.

Chicharro and colleagues[6] conducted a meta-analysis of 24 studies to review the prevalence and association between VPA-induced hyperammonemia and clinical symptom presentation. The study confirmed the prevalence of hyperammonemia among patients receiving VPA (16% to 100%) varies widely. Additionally, the authors found no association between elevated ammonia levels and clinical symptom presentation. The authors suggested that measuring serum ammonia levels in asymptomatic patients taking VPA is unnecessary and can cause diagnostic confusion. In summary, the authors concluded that VPA should not be discontinued based on hyperammonemia alone.

Finally, Chopra and colleagues[9] conducted a case series showing no clear correlation of onset or severity of VPA-induced hyperammonemia with length of VPA treatment, VPA dosage, serum VPA levels, and serum ammonia levels. Valproic acid discontinuation was the primary management of VPA-induced hyperammonemia.

This study's purpose is to evaluate if patients with VPA-induced hyperammonemia are appropriately identified for treatment based on their symptom presentation. Valproic acid is a first-line treatment option for bipolar disorder.[10] Labeling patients as VPA-intolerant limits their treatment options. To help reduce unnecessary pharmacological changes and unnecessary ammonia-level monitoring, this study sought to determine the most efficacious treatment for VPA-induced hyperammonemia.

Methods

Electronic medical records of adult patients admitted to a psychiatric unit at a community teaching hospital were reviewed from June 1, 2011, to June 30, 2016. The hospital's current bed capacity is 203 beds with 84 dedicated to behavioral health. The hospital currently has 10 attending psychiatrists. The number of beds and psychiatrists were relatively consistent throughout this time period. The hospital's institutional review board approved this study. Patients met inclusion criteria if they received at least 1 dose of any formulation of VPA or divalproex sodium during admission and had at least 1 ammonia level drawn during admission even if it was within normal limits. Patients admitted with cirrhosis diagnoses were excluded as cirrhosis can independently cause hyperammonemia.

This study's primary outcome was the prevalence of hyperammonemia in psychiatric patients on VPA who had at least 1 ammonia level drawn during admission. The secondary outcomes included the prevalence of symptomatic hyperammonemia and the prevalence and efficacy of various treatments for hyperammonemia in order to determine the most utilized and effective treatment modalities. This study compared the 6 interventions utilized by the hospital's physicians within the psychiatric setting: lactulose, levocarnitine, both lactulose and levocarnitine, VPA dose reduction, VPA discontinuation, and no treatment. Other treatments for hyperammonemia, such as rifaximin, metronidazole, and

TABLE 1: Baseline characteristics

Characteristic	n = 347
Male	232 (66.9%)
Median age	47 y
Age range	18–97 y
Intellectual disability[a]	84 (24.2%)
Concomitant topiramate use	2 (0.6%)
Admitting Diagnosis[b]	**n = 347 (%)**
Schizophrenia	111 (32.0)
Schizoaffective disorder	106 (30.6)
Dementia	78 (22.5)
Bipolar I disorder	74 (21.3)
Substance use disorder	47 (13.6)
Major depressive disorder	28 (8.1)
Seizure disorder	26 (7.5)
Bipolar II disorder	13 (3.8)
Personality disorder	7 (2.0)
Obsessive compulsive disorder	4 (1.2)
Generalized anxiety disorder	3 (0.9)

[a]Based on documented diagnosis of either intellectual disability (per *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition criteria) or mental retardation (per *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria) within the electronic medical chart.

[b]Note: One patient could have multiple admitting diagnoses.

neomycin, are not used at the study site for this indication.

This study defined hyperammonemia as greater than 47 µmol/L because this threshold is referenced within the institution's electronic medical record and may guide prescribers' clinical decisions.

Symptomatic hyperammonemia was defined as the documentation of any of the following keywords within a patient's electronic medical record: lethargy, altered mental status, confusion, stupor, delirium, disorientation, vomiting, or seizure. Only patients with multiple ammonia levels drawn during admission were used to determine treatment success rates. Treatments were deemed successful if ammonia levels were less than 47 µmol/L at discharge; the most recent ammonia levels were used for patients without ammonia levels drawn on their day of discharge. Decreases between initial and final ammonia levels were also calculated separately as percentages of initial levels.

Data collected via chart review included demographic information, admitting diagnoses, risk factors (intellectual disability, concomitant topiramate use), ammonia-level prescriber, length of stay, initial dose of VPA, first ammonia level drawn during encounter, presence of symptoms on day level drawn, and whether multiple ammonia levels were drawn during encounters. If multiple ammonia levels were drawn during admission, additional data was collected, including subsequent ammonia levels, final ammonia level prior to discharge, day during encounter at which level was within normal limits, and treatment modality chosen.

This study used chi-square tests of the independence of treatment modality and treatment success or failure, a secondary outcome. Mann-Whitney nonparametric tests compared percentage decreases in ammonia levels based on presence or absence of each treatment considered separately and also based on presence of each treatment versus no treatment. All other statistics were descriptive.

Results

Of the 357 patients screened, 347 patients met all inclusion criteria. Ten patients were excluded due to cirrhosis diagnoses on admission. Included patients' ages ranged between 18 and 97 years (median = 47 years); 66.9% were men. The most common admitting diagnoses were schizophrenia (32%) and schizoaffective disorder (30.6%). A complete list of baseline characteristics for the patient population appears in Table 1, which could include multiple admitting diagnoses for individual patients.

The primary outcome, reported prevalence of hyperammonemia in psychiatric patients on VPA who had at least 1 ammonia level drawn, was 36% (125/347). The prevalence of hyperammonemia symptoms among hyperammonemic patients was 43.2% (54/125). Patients with normal ammonia levels had more prevalent symptoms (64.9%, 144/222) than hyperammonemic patients, presumably due to causes other than hyperammonemia. This result highlighted the low specificity of symptoms that are potentially but not necessarily attributable to hyperammonemia.

Lactulose was the most common treatment (48.7%). Table 2 lists the secondary outcomes relating to treatment prevalence and success, which sometimes included multiple treatments for individual patients. Valproic acid discontinuation was most effective (56.3% success rate; mean percentage ammonia decrease = 27.4% versus 8.9% if not discontinued; Mann-Whitney $P = .07$). Levocarnitine treatment had a 50% success rate (mean decrease = 12.3% versus 14.8% without levocarnitine—ie, with other treatments or no treatment; $P = .73$). Lactulose treatment had a 41.8% success rate (mean decrease = 22.5% versus 6.2% without lactulose; $P = .29$). Receiving no treatment was least successful (29.2%

TABLE 2: Secondary outcome: treatment prevalence or success

Treatment[a]	Prevalence n (%)	Success[b] n (%)
Discontinuation of valproic acid	32/113 (28.3)	18/32 (56.3)
Levocarnitine	38/113 (33.6)	19/38 (50.0)
Lactulose and levocarnitine	19/113 (16.8)	9/19 (47.4)
Lactulose	55/113 (48.7)	23/55 (41.8)
Reduction of valproic acid dose	25/113 (22.1)	10/25 (40.0)
No treatment	24/113 (21.2)	7/24 (29.2)

[a]Note: One patient could have been initiated on several different treatment interventions during 1 admission.

[b]A treatment was deemed successful if the ammonia level was less than 47 µmol/L at discharge; if a patient did not have an ammonia level drawn on the day of discharge, then the most recent ammonia level was used for this outcome measure.

success rate). Of those untreated patients, 58% were asymptomatic. Untreated patients' ammonia levels increased by 7.6% on average, whereas the mean percentage decrease was 19.7% for patients receiving any treatment (Mann-Whitney $P=.02$). Differences in success rates were statistically insignificant between the most and least successful treatments ($\chi^2_1=3.05$, $P=.08$) and between treatments overall ($\chi^2_4=4.91$, $P=.30$). When comparing percentage changes in ammonia levels for each treatment versus no treatment, patients whose VPA was discontinued (sometimes in addition to other treatments) showed significantly more improvement than completely untreated patients (Mann-Whitney $P=.02$) as did patients who received lactulose (and sometimes other treatments; $P=.04$). There were no significant differences in ammonia-level changes between untreated patients and patients treated with levocarnitine ($P=.09$) or reduced VPA ($P=.13$).

Discussion

Although lactulose was the most common treatment, VPA discontinuation was most effective. These results compare well with published findings and demonstrate that many patients with hyperammonemia are asymptomatic. Based on previous studies, these patients may not require treatment. It remains unknown whether prolonged, asymptomatic hyperammonemia may eventually result in symptoms. Carnitine supplementation has been recommended during VPA therapy for seizure disorders in children at risk of developing carnitine deficiency, in VPA poisoning, and in VPA-induced hepatotoxicity.[11] It is unclear whether patients taking VPA for psychiatric indications may benefit from carnitine supplementation in the absence of hyperammonemia as prophylaxis.

Although this study provides data regarding the prevalence and treatment efficacies for VPA-induced hyperammonemia, causal conclusions are limited by its nonexperimental retrospective design. Ultimately, determining the true prevalence for VPA-induced hyperammonemia is difficult as not all patients on VPA had ammonia levels drawn. Furthermore, the lack of criteria specific to symptomatic hyperammonemia was a weakness of the study. The prevalence of symptoms was higher in patients with normal ammonia levels than among hyperammonemic patients. A unique finding regarding symptom presentation was that 34 of the 54 patients with elevated ammonia levels were admitted for dementia. Dementia and numerous psychiatric diagnoses and medications can cause confusion and other relevant symptoms. Clinicians also face this challenge in practice when determining if their patients are symptomatic and require treatment. Additionally, 18% (40/222) of patients with normal ammonia levels received treatment (ie, did not belong to the "no treatment" group), possibly as prescribed from previous hyperammonemia episodes. This may have led to overestimation of treatment efficacy as they were not hyperammonemic during admission. Another limitation is that adherence to various treatments was not measured. Common treatment regimens used in this hospital were levocarnitine 330 mg 3 times daily or lactulose 20 g to 30 g 3 to 4 times daily; however, patients may have refused medications, or lactulose could have been held (eg, for diarrhea), which may have reduced effectiveness of lactulose or levocarnitine therapy. Adherence rates could explain why the combination of levocarnitine and lactulose was no more effective than levocarnitine alone although this result could also reflect sampling error. Additionally, many patients received several different interventions during admission, which could confound success rates for specific treatments. Finally, the clinical debate regarding the upper limit of normal ammonia limited the study. Its definition was derived from the hospital's threshold for normal; however, if other facilities guide treatment with different thresholds, this could limit generalizability.

The study's large sample size was one strength. It is the largest study of VPA-induced hyperammonemia to date. In addition, a wide variety of psychiatric diagnoses and numerous prescribers were involved, which strengthens generalizability.

In conclusion, it is recommended that prescribers order ammonia levels for patients on VPA only when they are symptomatic. Prescribers should consider VPA discontinuation the primary treatment unless benefits of continued VPA treatment outweigh risks of sustained hyperammonemia. If VPA discontinuation is not clinically feasible, levocarnitine and lactulose may be similarly effective treatments within current psychiatric practice. This study could not find significant benefits of combining levocarnitine and lactulose treatments although statistical power was only sufficient to detect moderately large differences. Future directions may include prospective, randomized control trials directly comparing each intervention to further identify the most effective treatment modality for VPA-induced hyperammonemia, which may include exploring other ways to measure treatment efficacy.

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