

Hyperammonemia in patients receiving valproic acid in the hospital setting: A retrospective review

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Abstract

Introduction: Valproic acid (VPA) is widely used for the treatment of epilepsy, migraine, and a variety of psychiatric conditions. The reported incidences of hyperammonemia induced by VPA use is variable. The purpose of this study is to evaluate the incidence of VPA-induced hyperammonemia in the general adult inpatient population.

Methods: Adult patients who received at least 1 dose of VPA and derivatives between June 1, 2017 to December 31, 2017 were included. Patients were excluded if they did not have VPA administered during their inpatient stay or if they had elevated ammonia levels ($>33 \mu\text{mol/L}$) prior to initiation of VPA. Patients with a confirmed diagnosis of liver cirrhosis were also excluded. The primary endpoint was the incidence of hyperammonemia. Secondary outcomes included symptoms of hyperammonemia, diagnosis of VPA-induced hyperammonemia, and treatment of VPA-induced hyperammonemia.

Results: A total of 162 patients were included in this study. A total of 33 (20.4%) patients were identified as having the primary outcome of hyperammonemia; 26 (16.0%) patients had symptoms of hyperammonemia, and 13 (8.0%) patients were diagnosed with VPA-induced hyperammonemia. Treatment modalities included administration of lactulose, levocarnitine, discontinuing VPA, or decreasing the VPA dose.

Discussion: The administration of VPA in the general adult inpatient population resulted in a 20.4% incidence of hyperammonemia, with a lower rate of diagnosed VPA-induced hyperammonemia. Clinicians should be encouraged to obtain ammonia levels in patients receiving VPA if symptoms of altered mental status or encephalopathy develop.

Keywords: valproic acid, valproate, VPA, hyperammonemia

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Introduction

Valproic acid (VPA) is a medication used in the treatment of a variety of disease states including epilepsy, migraine prevention, and certain psychiatric conditions. Hyperammonemia is a known side effect of VPA and has been documented in several case reports.¹⁻¹² VPA-induced hyperammonemia is thought to be due to disruption of the urea cycle and resultant decrease in ammonia metabolism or by decreasing glutamate metabolism.^{13,14} While many patients with hyperammonemia remain asymptomatic, hyperammonemia can lead to somno-

lence, vomiting, ataxia, increased frequency of seizures, mental status changes, and coma.¹⁴ Hyperammonemia can occur with both acute and chronic VPA use.^{14,15} Identified risk factors for hyperammonemia include female sex, concomitant use of antiepileptic or antipsychotic medications, liver disease, presence of urea cycle disorders, increased doses of VPA, and increased serum VPA levels.¹⁴⁻¹⁶

Analyses investigating the incidence of hyperammonemia in adult populations treated with VPA have focused on patients with psychiatric disorders or epilepsy. The incidence of hyperammonemia reported in these studies ranged from 28% to 55%, while rates of symptomatic VPA-induced hyperammonemia were lower.¹⁶⁻²⁰ There are few analyses investigating the incidence rates of hyperammonemia in the general adult inpatient population, where VPA can be used for a variety of indications. This study seeks to describe the incidence of hyperammonemia in the general adult inpatient population receiving VPA.

Methods

This retrospective study was conducted at a 452-bed teaching hospital. Patients ≥ 18 years of age who were admitted to Intermountain Medical Center between June 1, 2017 and December 31, 2017 and who received at least 1 dose of VPA or derivatives during their admission were included in this study. Exclusion criteria included a VPA order that was not administered, diagnosis of liver cirrhosis, or an elevated ammonia level prior to initiation of VPA. Patients with a confirmed diagnosis of liver cirrhosis were excluded since hyperammonemia can occur independently of VPA in this patient population. Screening for patients who met inclusion criteria was conducted via retrospective review of inpatient medication administration records.

Approval to conduct this study was granted by the Intermountain Healthcare IRB. The primary outcome was the incidence of hyperammonemia among patients who received at least 1 dose of VPA or derivatives during their hospital admission. Hyperammonemia was defined as a new ammonia level above the upper limit of normal for the institution's reference range of 33 mcg/dL. The institution's laboratory protocol states that ammonia blood samples are immediately placed on ice and sent to the lab for processing within 15 minutes to ensure the integrity of the sample and accuracy of the result. Secondary outcomes included symptoms of hyperammonemia, diagnosis of VPA-induced hyperammonemia, and treatment of VPA-induced hyperammonemia. Symptoms of VPA-induced hyperammonemia were defined as altered mental status, encephalopathy, agitation, cognitive

TABLE 1: Characteristics of patients receiving valproic acid, N = 162

Patient Characteristics	Mean (Min-Max)
Age, y	55 (18-95) ^a
Weight, kg	85.5 (44.7-169.8)
BMI, kg/m ²	29.8 (14.9-75.0)
Albumin, g/dL (n = 114)	3.5 (1.6-4.8)
Ammonia, mcg/dL (n = 54)	44.2 (17-105)
Valproic acid level, mcg/mL (n = 78)	58.3 (0-146)
	n (%)
Male sex	100 (61.7)
Comorbid conditions	
Hypertension	74 (45.7)
Psychiatric conditions	65 (40.1)
Diabetes	37 (22.8)
Cerebrovascular disease	17 (10.5)
Chronic kidney disease	10 (6.2)
Liver disease (noncirrhosis)	2 (1.2)
Indications for valproic acid	
Seizures/epilepsy	90 (55.5)
Psychiatric condition	41 (25.3)
Agitation	9 (5.6)
Headache	4 (2.5)
Trigeminal neuralgia	1 (0.6)
Indication not documented	17 (10.5)

^aAge is referenced as median (min-max).

changes, lethargy, delirium, or disorientation identified through review of clinician documentation.

Other data collected included patient demographics (age, sex, and weight), risk factors for hyperammonemia (concomitant medications and comorbidities), VPA indications for use, and ammonia and VPA plasma levels. Concomitant medications included corticosteroids, salicylates, antipsychotics, and other antiepileptic medications. Comorbidities included noncirrhotic liver disease, diabetes, hypertension, cerebrovascular disease, psychiatric conditions, and chronic kidney disease.

The primary and secondary outcomes, with the exception of treatment of VPA-induced hyperammonemia, were calculated as incidence rates. The secondary outcome of treatment was reported as qualitative data.

Results

A total of 162 patients met inclusion criteria (Table 1). No patients were excluded. The median age was 55 years (min-max, 18-95 years), and most patients (61.7%) were male. The most common comorbid conditions included

TABLE 2: Characteristics of patients with hyperammonemia

Patient Characteristics	Patients With Hyperammonemia N = 33	Patients Without Hyperammonemia N = 129
	Mean (Min-Max)	
Age, y	55 (26-90) ^a	55 (18-95) ^a
Ammonia plasma level, mcg/dL	53.3 (27-105) n = 36	27.1 (17-33) n = 18
Valproic acid plasma level, mg/mL	61.6 (13.2-108.4)	55.5 (0-146)
	n (%)	
Male sex	20 (60.6)	81 (62.8)
Comorbid conditions		
Hypertension	13 (39.4)	61 (47.2)
Psychiatric conditions	12 (36.4)	53 (41.1)
Cerebrovascular disease	9 (27.3)	8 (6.2)
Diabetes	3 (9.1)	34 (26.4)
Chronic kidney disease	2 (6.1)	8 (6.2)
Selected concomitant medications		
Quetiapine	6 (18.2)	11 (8.5)
Aspirin	4 (12.1)	8 (6.2)
Topiramate	2 (6.1)	2 (1.6)
Lamotrigine	1 (3.0)	7 (5.4)
Phenytoin	1 (3.0)	3 (2.3)
Primidone	1 (3.0)	0 (0)
Lurasidone	1 (3.0)	0 (0)
Haloperidol	1 (3.0)	2 (1.6)
Olanzapine	1 (3.0)	12 (9.3)

^aAge is referenced as median (min-max).

hypertension (45.7%), psychiatric illness (40.1%), and diabetes (22.8%). The most common indications for VPA were seizures or epilepsy (55.5%), psychiatric illness (25.3%), and agitation (5.6%).

A total of 33 (20.4%) patients were identified as having hyperammonemia after administration of VPA. However, only 13 (8.0%) of these patients were diagnosed with hyperammonemia secondary to VPA. The mean ammonia level for the patients diagnosed with VPA-induced hyperammonemia was 64.3 mcg/dL compared to 49.1 mcg/dL for those patients with hyperammonemia without a diagnosis of VPA induced hyperammonemia. Twenty-six (16.0%) patients were considered to have symptomatic hyperammonemia. The average plasma ammonia level for symptomatic patients was 55.4 mcg/dL compared to 50.2 mcg/dL for patients with hyperammonemia without symptoms. Of the 13 patients diagnosed with VPA-induced hyperammonemia, 12 patients were observed to be symptomatic. All 13 patients diagnosed with VPA-induced hyperammonemia were treated with either monotherapy or combination therapy with the following:

lactulose (n = 7, 53.8%), levocarnitine (n = 3, 23.1%), dose reduction of VPA (n = 1, 7.7%), or VPA discontinuation (n = 3, 23.1%).

Table 2 highlights differences between the patients who developed hyperammonemia compared to those that did not. Of the patients meeting the primary outcome, 20 (60.6%) were male. The mean ammonia plasma level was 53.3 mcg/dL (min-max, 27-105 mcg/dL) and the mean VPA plasma level was 61.6 mcg/mL (min-max, 13.2-108.4 mcg/mL). There was 1 patient with an ammonia plasma level below the reference range of 33 mcg/dL. This level was upon repeat of the lab and the patient initially had an elevated ammonia level. The decrease in ammonia level was not explained by any medical interventions such as discontinuation of the medication or dosage adjustments. The most common comorbid conditions seen in patients with hyperammonemia included hypertension (39.4%), psychiatric conditions (36.4%), and cerebrovascular disease (27.3%). Selected concomitant medications are outlined in Table 2. These medications were found for 17 patients.

Discussion

Hyperammonemia associated with VPA administration is an already known adverse drug effect in the literature. However, the majority of the literature focuses on 1 predisposing disease state, specific patient population, or detailed case reports. This study provides unique insight into the incidence of VPA-induced hyperammonemia among general hospitalized adults.

The patients who developed hyperammonemia after VPA administration were similar in terms of age and sex to the patients who received VPA but did not develop hyperammonemia in this study. The prevalence of hypertension, psychiatric diagnoses, and chronic kidney disease in the hyperammonemic patients were also similar, but the prevalence of cerebrovascular disease in patients who developed hyperammonemia was higher. Common risk factors for VPA-induced hyperammonemia are female sex and hepatic disease, but the opposite was seen in this study. Hyperammonemia occurred more often in males and neither patient with hepatic disease had hyperammonemia. Only 13 of the 33 patients who developed hyperammonemia were diagnosed with hyperammonemia secondary to VPA administration. These patients had a higher overall mean ammonia plasma level than those without a diagnosis of VPA-induced hyperammonemia.

A similar study by Baddour and colleagues¹⁷ was performed in patients admitted to a psychiatric medicine unit. The rate of hyperammonemia seen in that study was 36%, which is higher than the rate seen in this retrospective analysis. This could be explained by the fact that in the former study, only patients with at least 1 ammonia level drawn were included. It was decided to include all patients who received VPA, regardless of if an ammonia level was drawn, to reflect clinical practice where an ammonia level might not be drawn unless the patient is symptomatic.

Previous studies have varied in how symptomatic hyperammonemia is reported. Baddour and colleagues¹⁷ reported in their study that 43.2% of patients who developed hyperammonemia were symptomatic. In our analysis, 78.8% of the patients with hyperammonemia were symptomatic. This difference could be explained by the increased frequency of obtaining an ammonia level in general hospitalized adults suspected of symptomatic hyperammonemia.

In another analysis performed by Lewis and colleagues¹⁸ in hospitalized patients with at least 1 psychiatric diagnosis, the rate of VPA-induced hyperammonemic encephalopathy reported was 2.5%. Comparatively, in our study, 7.4% of patients were diagnosed with symptomatic VPA-induced hyperammonemia. However, in the study

performed by Lewis and colleagues,¹⁸ only patients with at least 1 psychiatric diagnosis were included, so some patients with hyperammonemia but no psychiatric diagnosis were excluded. Additionally, the reference range used was higher than the reference range used in our study.

This study also provides insight on the treatment of VPA-induced hyperammonemia. Similar to other studies,^{17,18} lactulose was a frequent treatment choice. In this study, about 25% of patients had VPA discontinued. This is similar to what was seen in Baddour and colleagues (28.3%),¹⁷ but lower than what was found in Lewis and colleagues (approximately 40%).¹⁸

Another aspect that should be discussed is that the incidence seen in patients with formally diagnosed VPA-induced hyperammonemia (8.0%) is lower than both the rates of hyperammonemia (20.4%) and symptomatic hyperammonemia (16.0%). In some of the cases of hyperammonemia that was not diagnosed as VPA-induced, either the hyperammonemia or the altered mental status was attributed to another cause, or the elevation in ammonia was not considered clinically relevant. Another possible explanation is that hyperammonemia as a side effect of VPA may not be recognized.

A limitation to this study is the retrospective design, which limits the ability to demonstrate causality. Additionally, because of the retrospective nature of this analysis, we cannot be certain the proper laboratory protocol was carried out when handling ammonia samples and this may affect the reliability of the results. Another limitation is that data on prior use of VPA was not collected, therefore, duration of VPA use in this population is unknown. Additionally, the total daily doses of VPA were not recorded to determine if VPA-induced hyperammonemia was dose-dependent. Since serum ammonia levels were not collected from every patient, only those who were symptomatic, the true incidence of hyperammonemia could also be underestimated. While information was collected regarding the treatment modalities used, the effectiveness of each treatment was not recorded.

The strengths of this study include the sample size, which is larger than previous studies.^{17,18} Another strength is that the population includes general hospitalized adults, rather than limited based on type of unit or indication for VPA. This offers wider applicability of the study.

Conclusion

In this study of general hospitalized adults who received VPA, 20.4% developed hyperammonemia. The overall rate

of symptomatic hyperammonemia was 16.0%. Only 8.0% of patients were diagnosed with VPA-induced hyperammonemia, possibly because of limited clinical relevance of symptoms, alternate causes, or under-recognition of this adverse drug effect. Clinicians should be encouraged to obtain ammonia levels in patients receiving VPA if symptoms of altered mental status or encephalopathy develop. Future studies should investigate the correlation between identifiable risk factors for hyperammonemia and its incidence, and the effectiveness of treatments for VPA-induced hyperammonemia.

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