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ORIGINAL ARTICLE

Hyperammonemia in patients on Valproic Acid therapy in a tertiary care hospital of Karachi

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ABSTRACT

OBJECTIVE: To assess the incidence of hyperammonemia in patients receiving valproic acid (VPA) therapy.

METHODS: This cross-sectional study was conducted at the Department of Neurology, Ziauddin Medical University and Hospital, Karachi, for six months from April to October 2019. A total of 158 patients of both genders, aged between 18 to 80 years, presented in emergency with complaints of seizures and who had received a minimum dose of valproic acid before blood withdrawal were included. Pregnant women, patients with cirrhotic liver, or chronic renal impairment were excluded from the study.

RESULTS: Out of 158 patients, 80 (50.6%) were females and 78 (49.4%) were males. Mean age of patients was 55.53±18.26 years. Among the participants, 27 (17.1%) had undergone VPA therapy for 30 days or more, while 131 (82.9%) had received it for less than 30 days. The mean duration of VPA therapy was 8.58±10.41 days. Among the 158 patients, 95 (60.1%) with seizures receiving VPA treatment were diagnosed with hyperammonemia. The mean serum ammonia level was 66.50±44.59 mg/dL, and mean VPA dose administered was 1000±125 mg/day. There was a statistically significant association between the dose of VPA and the incidence of hyperammonemia ($p < 0.05$). Patients receiving a daily dose of VPA exceeding 1000 mg were more likely to develop hyperammonemia.

CONCLUSION: This study revealed a high incidence of hyperammonemia among patients undergoing VPA therapy, with 60.1% of the total patients receiving VPA therapy experiencing hyperammonemia.

KEYWORDS: Seizures (MeSH); Valproic Acid (MeSH); Valproic acid therapy (Non-MeSH); Hyperammonemia (MeSH).

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INTRODUCTION

Valproic acid (VPA) is a treatment for bipolar disorder that is frequently prescribed due to its effectiveness in regulating mood. However, using it could result in hyperammonemia as a negative effect. When the urea cycle is disturbed, it can cause hyperammonemia, which raises ammonia levels in the blood. Lethargy, vomiting, and changes in mental state are some symptoms that this disorder might present with. If left untreated, it can escalate to a life-threatening encephalopathy. Healthcare professionals face difficulties managing VPA-induced hyperammonemia because high ammonia levels are not necessarily associated with symptoms or abnormal liver function tests.[1]

It offers important advantages in mood stabilization, but on the other hand, its connection to hyperammonemia is recognized as a concern. N-acetyl glutamate, a vital part of the urea cycle, is inhibited in the mechanism of VPA-induced hyperammonemia, which raises ammonia levels in the blood.[2] Concurrent usage of drugs like topiramate, urea cycle issues, intellectual impairments, and carnitine deficiencies are risk factors for VPA-induced hyperammonemia.[3] The permissible range of ammonia levels is also a topic of ongoing discussion, with some institutions advocating levels as low as 30 mol/L and others as high as 60 mol/L.[4]

Prior investigations have revealed significant variation in the reported prevalence of hyperammonemia related to the use of valproic acid (VPA) therapy, ranging significantly from 2% to 80%.[5-7] A more comprehensive picture has been provided by recent studies, which show that the incidence of hyperammonemia can range from 0% to 56% in patients receiving VPA monotherapy.[5-7] This considerable discrepancy in reported incidence can be partially explained by differences in the classification criteria and definitions utilized for hyperammonemia among research studies. A case report of a 44-year-old man who developed Hyperammonemic Encephalopathy after receiving long-term Valproic Acid therapy has surfaced locally.[8] Additionally, an observational study carried out at Civil Hospital has confirmed that Valproic Acid might cause symptomatic hyperammonemia that results in encephalopathy, even in those within the recommended dose range and blood levels.[9] As a result, it's vital to constantly monitor patients using valproic acid for the illness, especially those who exhibit encephalopathic symptoms.

Despite the well-established link between VPA and hyperammonemia,

Table I: Demographic characteristics of patients (n=158)

Variables		Frequency	Percentage
Age (years)	< 50	59	37.3
	≥ 50	99	62.7
Gender	Female	80	50.6
	Male	78	49.4
Co-Morbids	Hypertension	91	57.6
	Diabetes Mellitus	67	42.4

Table II: Association of hyperammonemia with respect to patient's characteristics (n=158)

Variables			Hyperammonemia		p-value
			Present [n (%)] (n=95)	Absent [n (%)] (n=63)	
Age		< 50 years	32 (54.2)	27 (45.8)	37.3
		≥50 years	63 (63.6)	36 (36.4)	
Gender		Male	50 (64.9)	27 (35.1)	62.7
		Female	45(55.6)	36(44.4)	
Co- Morbids	Diabetes Mellitus	Yes	40 (59.7)	27 (40.3)	50.6
		No	55 (60.4)	36 (39.6)	
	Hypertension	Yes	53 (58.2)	38 (41.8)	49.4
		No	42 (62.7)	25 (37.3.4)	
Dose of Valproic Acid		>1000 mg/day	65 (67.7)	31 (32.3)	57.6
		< 1000 mg/day	30 (48.4)	32 (51.6)	
Duration of Valproic Acid		30 days or more	19 (70.4)	08 (29.6)	42.4
		< 30 days	76 (58.0)	55 (42.0)	

*p<0.05 is considered statistically significant.

several important knowledge gaps remain. Firstly, uncertainty persists regarding appropriately identifying and managing patients with VPA-induced hyperammonemia, particularly when they present asymptomatically or exhibit normal liver function. Secondly, the optimal treatment approach for this condition remains ambiguous. While discontinuation of VPA is recommended in cases of hyperammonemia, the comparative effectiveness of alternative treatments, such as lactulose and levocarnitine, in relation to discontinuation remains inadequately explored.

Given the limited availability of local data, this study aimed to ascertain the incidence of hyperammonemia among patients with seizures treated with Valproic acid (VPA) therapy.

METHODS

This cross-sectional study was conducted at the Department of Neurology, Ziauddin Medical University and Hospital in Karachi for a period of six months, from April to October 2019. A total of 158 patients of both genders, aged 18 to 80 years, who presented in the emergency department with complaints of seizures and had received at least one dose of valproic acid before blood withdrawal were included using a non-probability consecutive technique. Pregnant women, patients with cirrhotic liver, or chronic renal impairment were excluded from the study.

The ethical approval was obtained from the ethical review board of Dr. Ziauddin Hospital (Ref: NEU-2017-201-417 dated 11th April 2019). A written informed consent was obtained from each participant before their inclusion in the study. The primary outcome was to assess the incidence of hyperammonemia among patients receiving VPA therapy. As per the institutional protocols, the temperature of ammonia blood samples was immediately maintained and delivered to the lab for processing within 15 minutes to guarantee the integrity of the sample and the correctness of the result. For individuals receiving sodium valproate therapy, pre-dose valproic acid (VPA) levels were assessed. The secondary aim was to assess the association of hyperammonemia with the patient's characteristics. Other collected data included demographic information, Age, Dose of VPA, Duration of VPA used, gender, and co-morbid conditions.

The collected data were analyzed using SPSS Version 21.0. Descriptive statistics, such as mean ± standard deviation (SD), were calculated for variables including age, serum ammonium level, and dose of valproic acid. Frequency and percentage distributions were determined for categorical variables such as age group, gender, comorbidities, and hyperammonemia. The chi-square test was applied to assess the association between hyperammonemia and patient characteristics, where $p \leq 0.05$ was considered statistically significant.

RESULTS

Out of 158 patients with seizures on valproic acid, majority (n=99; 62.7%) were aging ≥ 50 years of age (Table 1). The mean age of patients was 55.53 ± 18.26 years (range 18-80) years. The mean serum ammonia level was 66.50±44.59 (range 15-240) mg/dL, and the mean dose of VPA was 1000±125 mg/day with a mean duration of VPA used was 8.58±10.41 days.

Distribution of hyperammonemia after the dose of VPA revealed that 95 (60.8%) patients with seizures on VPA drugs were diagnosed to have hyperammonemia, whereas 63 (39.9%) had no hyperammonemia.

Table II presents the association between hyperammonemia and various patient characteristics. Among all other variables, a statistically significant association was observed between the dose of VPA and hyperammonemia ($p < 0.05$). Patients taking a daily dose of VPA > 1000 mg were more likely to have hyperammonemia.

DISCUSSION

Hyperammonemia associated with VPA administration is a well-documented adverse drug effect in the existing

literature. However, much of the available research has been focused on specific disease conditions, particular patient groups, or detailed case reports. This study brings a unique perspective by examining the incidence of hyperammonemia in a broader spectrum of patients undergoing VPA therapy.

Our study found that 60.1% of patients developed hyperammonemia during VPA treatment, which is higher than the prior research. Baddour and colleagues conducted a study in patients admitted to a psychiatric medicine unit and reported a 36% rate of hyperammonemia,[10] higher than the rate observed in a retrospective analysis (20.4%). Similarly, Tseng et al. reported a 27.8% incidence of hyperammonemia associated with VPA therapy, with severe hyperammonemia (more than 150 μg/dL) occurring in 5.1% of cases.[11] Another analysis by Lewis and colleagues focused on hospitalized patients with at least one psychiatric diagnosis reported a 2.5% rate of VPA-induced hyperammonemic encephalopathy.[12] It's worth noting that their study included only patients with psychiatric diagnoses, potentially excluding some individuals with hyperammonemia but no psychiatric diagnosis. Furthermore, their reference range for ammonia levels was higher than the one used in our study.

Notably, our study found that patients who developed hyperammonemia exhibited similarities concerning age, gender, and the presence of conditions such as hypertension and diabetes. These findings align with the research conducted by McMorris et al., which also reported no statistically significant differences in these variables among hyperammonemic patients.[13] Moreover, they also observed similarities in terms of psychiatric diagnoses and the presence of chronic kidney disease in patients who experienced hyperammonemia. This implies that while various demographic and clinical factors were comparable between hyperammonemic and non-hyperammonemic patients, the presence of cerebrovascular disease emerged as a distinctive factor associated with hyperammonemia in their cohort. Additionally, it's worth noting that several studies have consistently supported a connection between elevated ammonia levels and VPA dosage, alongside other contributing factors such as malnutrition, female gender, concurrent use of other antiepileptic drugs (AEDs), and antipsychotic medications.[5,14] These factors collectively contribute to understanding the complex relationship between VPA therapy and hyperammonemia.

Similar to this, research at Oslo University Hospital examined the effects of intravenous (IV) VPA-induced hyperammonemia on the management of epilepsy. The medical records of 31 adult patients who received IV VPA for the treatment of epilepsy and were over the age of 18 were examined as part of this investigation. Thirty of these individuals had increased ammonia levels while receiving IV VPA; 16 of them stopped using VPA as a result, while six had their doses decreased. The results of this study showed that ammonia levels significantly decreased after VPA dosage modifications, highlighting the significance of carefully monitoring and controlling drug dosage in patients receiving IV VPA.[16] Importantly, the present study results were in line with the aforementioned research, further confirming the relationship between VPA dosage and ammonia levels. Specifically, our study revealed that among patients receiving doses exceeding 1000 mg/day, 67.7% exhibited higher ammonia levels, providing strong evidence of a dose-dependent effect of VPA on ammonia levels ($p=0.015$). These findings emphasize the necessity of vigilant dose monitoring when utilizing VPA therapy to minimize the risk of hyperammonemia-associated complications.

Our study's main limitation was the lack of documentation of the total daily dosages of VPA, which would have been essential for determining if the emergence of VPA-induced hyperammonemia was related to dose.

CONCLUSION

According to this study, 60.1% of all patients receiving VPA therapy had hyperammonemia. This emphasizes how essential it is for medical professionals to be cautious about assessing ammonia levels in patients receiving VPA medication, especially when symptoms of encephalopathy or altered mental status appear. The association between observable risk factors for hyperammonemia and its occurrence should be investigated in further studies, and the effectiveness of therapies for VPA-induced hyperammonemia should be evaluated.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

IA: Concept and study design, acquisition of data, drafting the manuscript, approval of the final version to be published

BAS: Acquisition of data, critical review, approval of the final version to be published

FK: Analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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