Brief Communication

Influence of valproate-induced hyperammonemia on treatment decision in an adult status epilepticus cohort

Sarah Folkestad Habhab, Line Bédos Ulvin, Erik Taubøll, Sigrid Svalheim, Ketil Berg Olsen, Morten Andreas Horn, Kjell Heuser

Abstract

Introduction: Status epilepticus (SE) is a neurological emergency in which immediate intervention is required to prevent permanent brain damage and death. Intravenous (IV) valproic acid (VPA) is often used for the treatment of SE. However, IV VPA frequently increases the blood ammonia level. In this study, we explore the impact of IV VPA-induced hyperammonemia (HA) on treatment management of SE and discuss the challenges related to this particular condition.

Methods: We used data from medical records of 31 adult patients (≥18 years) treated with IV VPA for SE at Oslo University Hospital between January 2006 and October 2019. Clinical and blood sample data and information about the influence of HA on treatment were collected. Correlations between ammonia levels and other continuous or categorical variables were tested using the Pearson’s correlation coefficient. The Kruskal–Wallis H-test was used to analyze associations between different variables and treatment decisions.

Results: Thirty of 31 patients had increased ammonia levels during IV VPA treatment. In 16/30 patients, VPA was discontinued, and in 6/30 patients, the dose was reduced. We found a difference in the median peak ammonia level among the groups where VPA was discontinued (99 μmol/l), reduced (71 μmol/l), and continued (55.5 μmol/l) (P = 0.008). Also, clinical status, measured by West Haven Criteria, varied among the groups where VPA was discontinued (3.5), reduced (2.5), and continued (2.0) (P = 0.01). Treatment decisions at peak ammonia were not associated with the level of liver enzymes and bilirubin.

Conclusion: Hyperammonemia had a substantial impact on further management. To date, no recommendations exist on how to manage VPA-induced HA in SE. We call for systematic prospective studies and evidence-based guidelines.

Keywords: Epilepsy, Valproate, Ammonia, Hyperammonemia, Treatment decision, Outcome

1. Introduction

Status epilepticus (SE) is a neurological emergency that can lead to permanent brain damage and death [1]. Rapid and aggressive treatment is important and should be given according to a staged protocol [2]. Today, intravenous (IV) benzodiazepine is the first drug of choice and is expected to terminate SE in up to two out of three cases [3]. When benzodiazepines fail, phenytoin or valproic acid (VPA) is commonly used as second-line treatment [3].

An established adverse effect of VPA is an increase of the blood ammonia level that may occur in both chronically or acutely treated patients [4,5]. While a few studies and recommendations exist on how to handle VPA-associated hyperammonemia (HA) in patients receiving chronic peroral treatment with VPA [5,6], no guidelines are available on how to manage this adverse effect in patients with SE.

The aim of this study was to evaluate the prevalence and level of HA induced by IV VPA in an adult cohort with SE, its impact on treatment decisions, and to discuss challenges related to this particular condition.

2. Methods

2.1. Data collection

In this retrospective observational study, we included 31 randomly chosen adult patients (≥18 years) who were treated for SE at Oslo University Hospital (OUS) between January 2006 and October 2019. Inclusion criteria were (1) patients with SE according to the International League Against Epilepsy (ILAE) latest definition [7], who were
(2) treated with IV VPA, and (3) tested for blood ammonia level. We reviewed the medical records and registered ammonia levels after start of VPA infusion, including peak ammonia level. The OUS reference value for ammonia is <32 μmol/l, and values higher than this were considered as an increase. We classified ammonia levels (μmol/l) as follows: normal level: 0–32; mild increase: 33–60; moderate increase: 61–100, and marked increase: >100. This classification was done because of discretionary assessment, as no established graduation exists.

Measurement of ammonia, liver enzymes, and VPA was all done according to the OUS best practice procedures for safe and accurate blood sampling. Venous blood draw was performed for all tests, usually between hrs 06 AM and hrs 09 AM. To assess intercurrent liver injury, we collected data on bilirubin and liver enzymes: alanine transaminase (ALAT), aspartate transaminase (ASAT), Gamma-glutamyl transferase (GGT), and Alkaline phosphatase (ALP). Further, VPA serum concentration from the same day as peak ammonia level was collected for analysis.

Information about mental status and grade of consciousness at the day of peak ammonia level was used to retrospectively assess the West Haven score [8]. The West Haven score is a clinical five-point classification system which is primarily used for hepatic encephalopathy [9].

To evaluate the influence of increased ammonia level on the decision on further treatment, the patient records had to have a clear statement on the time point and motivation for VPA dose reduction or cessation.

2.2. Data analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) Statistics for Macintosh, version 25.0 and version 26.0 (Armonk, NY: IBM Corp.). Frequencies are expressed in numbers and percentages. For the descriptive analysis, we used the median and the quartile deviation (QD). Scatter graphs were plotted between ammonia blood levels and other variables. Correlations between ammonia levels and other continuous or categorical variables were tested using the Pearson’s correlation coefficient. The Kruskal–Wallis H-test was used to analyze associations between different variables and treatment decisions.

2.3. Study settings and ethics

The study was conducted by the Epilepsy Research Group of Oslo (ERGO), Department of Neurology, OUS, Oslo, Norway. It was approved by the Data Protection Official of OUS and is a part of a larger quality control study [10].

3. Results

3.1. Patient characteristics

Patient characteristics are summarized in Table 1. We identified a total of 31 patients who fulfilled the inclusion criteria. The median age was 62 years (QD = 13.5), and 17 were women. The median number of other antiepileptic drugs (AEDs) at the same day as the peak ammonia level was two (QD = 1). Nine patients were treated with VPA before admission, one patient had a diagnosis of having subcapsular hepatic shunt, and seven patients had a history of alcohol misuse.

3.2. Laboratory results

Laboratory results are summarized in Table 1. Thirty of 31 patients had increased ammonia levels. The median peak ammonia level was 72 μmol/l (QD = 28.5). The median time interval from VPA infusion to peak ammonia was two days (QD = 1.5). The median time interval from VPA infusion to the first ammonia measurement was one day (QD = 1) with a firstly measured median ammonia value of 37 μmol/l (QD = 19).

Twenty-three patients had accurate information about the maintenance dose of VPA, and the median dose was 100 mg (QD = 0) per hour. The median VPA blood concentration at peak ammonia level was 532 μmol/l (QD = 114.88). Median VPA concentration within +/− three days from peak ammonia was 679 μmol/l (QD = 167). There was no correlation between peak ammonia and VPA concentration (r = +0.083, P = 0.661) (Fig. 1).

Liver enzymes were normal for all patients at the same day and within three days post and prior to the measured peak ammonia level. Correlations are visualized in Fig. 1. No correlation was seen between peak ammonia and liver parameters, except from GGT (r = 0.391, P = 0.036). We also compared biochemical markers in patients with normal and mildly increased ammonia level to the group with markedly increased ammonia level. In both groups, the biochemical markers were within normal range, except from ASAT that was only slightly increased in the group of markedly increased ammonia level.

3.3. Clinical status measured by West Haven Criteria

The distribution of West Haven grades in our patients is presented in Table 1. Out of 31 patients, one had a West Haven grade 0, four grade 1, eight grade 2, eight grade 3, and 10 grade 4. We found a correlation between peak ammonia level and West Haven grade (r = 0.467, P = 0.008).

3.4. Impact of ammonia levels on treatment decisions

Associations between different clinical and biochemical variables and treatment decisions are presented in Table 2. In 16 out of 30 patients, VPA treatment was discontinued, and in 6, the VPA dose was reduced. Two patients received treatment with lactulose for increased ammonia levels.

| Table 1 | Patient characteristics. |
| --- | --- |
| Clinical and epidemiological data |  |
| Gender M/F (%) | 14/17, (45%/55%) |
| Age, Y (QD) | 62 (13.5) |
| Already on VPA therapy, N (%) | 9 (29%) |
| History of liver disease, N (%) | 1 (3%) |
| History of alcohol misuse, N (%) | 7 (23%) |
| VPA dose, level (QD) |  |
| Loading dose (N = 21) | 2100 mg (675) |
| Maintenance dose (N = 23) | 100 mg/h (0) |
| Blood concentration of ammonia (μmol/l), N (%) |  |
| Normal (0–32) | 1 (3%) |
| Mild increase (33–60) | 9 (29%) |
| Moderate increase (61–100) | 12 (39%) |
| Marked increase (>100) | 9 (29%) |
| Median ammonia concentration (μmol/l) |  |
| Median peak level (QD) | 72 (28.5) |
| Median first level (QD) | 57 (19) |
| Biochemical markers at peak ammonia, level (QD) |  |
| Serum-VPA (μmol/l) (N = 30) | 532 (114.9) |
| ALAT (U/L), normal 10–70 (N = 31) | 21 (13) |
| ASAT (U/L), normal 15–45 (N = 30) | 30 (15.4) |
| GGT (U/L), normal 15–115 (N = 29) | 60 (28) |
| ALP (U/L), normal 35–100 (N = 29) | 56 (18) |
| Bilirubin (μmol/l), normal 5–24 (N = 28) | 6 (3.5) |
| West Haven grade at peak ammonia, N (%) |  |
| 0 = potentially mild decrease in intellectual ability and coordination | 1 (3%) |
| 1 = trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction | 4 (13%) |
| 2 = lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior; | 8 (26%) |
| 3 = somnolence to semistupor but responsive to verbal stimuli; confusion; gross disorientation | 8 (26%) |
| 4 = coma | 10 (32%) |

Values are represented in number of patients (N) or medians. M = male, F = female, y = years, QD = quartile deviation. VPA, valproic acid; ALAT, alanine transaminase; ASAT, aspartate transaminase; GGT, gamma glutamyltransferase; ALP, alkaline phosphatase.
There was a significant difference in the median peak ammonia level among the groups where VPA was discontinued (99 μmol/l), reduced (71 μmol/l), and continued (55.5 μmol/l) (P = 0.008). Also, there was a significant difference in the median West Haven grade among the groups where VPA was discontinued (3.5), reduced (2.5), and continued (2.0) (P = 0.01). We could not observe an association between treatment decisions at peak ammonia and the level of liver enzymes, bilirubin, or VPA concentration.

Treatment decisions at peak ammonia were independent of the level of liver enzymes or bilirubin. Biochemical markers for liver failure were normal for all patients, and the increase of ammonia level was independent of the serum concentration of VPA. Treatment decisions were not done by means of any protocol.

4. Discussion

4.1. Results in context

We here investigate the impact of the blood ammonia level on treatment decisions in patients with SE treated with IV VPA. Hyperammonemia was a very common finding in these patients. We found that the blood ammonia level was independent of the serum concentration of VPA and, except from slight and infrequent aberrations, not associated with increase of liver enzymes or bilirubin. We observed that HA had a substantial impact on the management of antiepileptic treatment. Treatment decisions were not done by standard procedures.

Valproic acid-induced HA is a well-known phenomenon. Cross-sectional studies suggest a prevalence of 16 to 100 percent while prospective studies report on 70 to 100 percent [5,6]. However, existing publications on VPA-related HA are performed in patients who use VPA on a regular basis for either epilepsy or psychiatric disorders. For this group of patients, most authors recommend that ammonia should only be measured when symptoms of encephalopathy develop [4–6], which occurs infrequently [11].

Only sparse information is available on how to manage VPA-induced HA in SE. To our knowledge, only one recent study highlights HA specifically in patients with SE [12]. The authors recommend that VPA should be discontinued in cases of increased ammonia levels but do not provide any guidelines for measurement routines or specific interventions based on the level of increase. Further, there is no information on differences between acute or chronic VPA treatment, ammonia levels, guidelines for measurement, and clinical consequences.

Despite a careful literature search, we were not able to find any publication on the outcome of patients with SE with increased versus normal blood ammonia levels. This begs the question on what basis VPA is reduced or discontinued for the majority of patients with SE.

One obvious challenge for treating physicians is the lack of specific clinical signs or symptoms of encephalopathy. We found a correlation between ammonia levels and the severity of West Haven grade measuring signs of encephalopathy in our study cohort [8,9]. However, we experienced difficulties with the grading as the clinical symptoms assessed all may appear in SE per se. Moreover, sedative medications or postictal symptoms may mimic symptoms of encephalopathy.

Encephalopathy can be detected by electroencephalography (EEG) typically presenting with irregular, continuous, severe, and diffuse slowing with a predominance of rhythmical theta and delta activity.

Fig. 1. Serum concentration of valproate, liver enzymes, and bilirubin at peak ammonia level.
Table 2
Association between treatment decisions and biochemical and clinical variables in patients with SE with VPA-induced HA.

| Variables                      | Discontinued dose (N = 16) | Reduced dose (N = 6) | Continued (N = 8) |
|--------------------------------|-----------------------------|----------------------|-------------------|
| Biochemical parameters         |                             |                      |                   |
| Ammonia level (μmol/l)         | 99 (42.5)                   | 71 (10.1)            | 55.5 (15.6)       |
| VPA concentration (μmol/l)     | 545 (215.5)                 | 587 (166.9)          | 518.5 (102.8)     |
| West Haven grade               | 3.5 (0.5)                   | 2.5 (1.6)            | 2 (0.0)           |
| Bilirubin (μL/L)               | 5.5 (3.6)                   | 6.5 (2.1)            | 8 (5.13)          |
| ALAT (U/L)                     | 23 (13.3)                   | 17 (7.8)             | 17.5 (10.0)       |
| AST (U/L)                      | 36.5 (17.9)                 | 20 (12.7)            | 30 (8.5)          |
| ALP (U/L)                      | 56 (26.6)                   | 75 (75.5)            | 57 (11.8)         |
| GGT (U/L)                      | 56.5 (30.1)                 | 63 (60)              | 56 (31.0)         |
| Basis for treatment change, N (%) |                          |                      |                   |
| HA alone                       | 9 (30)                      | 6 (20)               |                   |
| HA + increased ser-VPA         | 2 (6.6)                     |                      |                   |
| HA + reduced consciousness     | 2 (6.6)                     |                      |                   |
| HA + increased liver enzymes   | 1 (3.3)                     |                      |                   |
| Lack of efficacy               | 1 (3.3)                     |                      |                   |
| Increased ser-VPA alone        | 1 (3.3)                     |                      |                   |

Presented variables at time peak of ammonia. Values are expressed in number of patients or median value (QD). P-values are considered statistically significant if \( P < 0.05 \). N = number of patients, QD = quartile deviation, HA = hyperammonemia, ser = serum; VPA, valproic acid; ALAT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyltransferase; ALP, alkaline phosphatase.

[13–15]. Although these phenomena also may occur in SE or during the postictal state, continued or regular periodic EEG after IV VPA administration and during the stabilization period of SE would, together with clinical observation and repetitive ammonia measurement, be advantageous to identify a potential ammonia-induced encephalopathy, as earlier encouraged by Trinka et al. [16].

4.2. Limitations

Data are generated from a cohort of retrospectively, nonsystematically recruited patients, which also means that laboratory tests were not performed according to a predefined protocol. Thus, time variation from the first administration of IV VPA to ammonia level measurement may have occurred. Furthermore, ammonia levels were not routinely measured prior to SE treatment, thus we cannot rule out that HA was present and unrelated to IV VPA treatment. We found a higher incidence of VPA associated ammonia increase than formerly described [4–6,12]. This may be due to differences in data acquisition. All our patients received high IV doses of VPA commonly together with other AEDs which both have been described as risk factors for increased ammonia levels [4,13,17]. Further, there is no established consensus on whether ammonia under VPA therapy should be measured or not. Therefore, it is possible that clinicians who monitored ammonia did this based on a clinical suspicion of ammonia toxicity, thus skewing the material towards changing VPA treatment regime.

5. Conclusion

In conclusion, our findings indicate that VPA-associated HA has a high impact on treatment decisions in SE. Treatment adjustments or discontinuation of VPA occur while no guidelines exist, and even without a common agreement on whether ammonia should be measured at all. This uncertainty may have an effect on the final outcome and could result in patients not being treated with an effective drug for a potentially life-threatening condition. To date, it seems to be a general consideration to taper or discontinue VPA to be on the safe side in the absence of appropriate clinical observation tools. Our study should be regarded as an eye opener and contribution to the discussion but is not suited to give any advises. We call for larger systematic and prospective studies generating definite evidence-based recommendations.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Bertramman JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol. 2015;14: 615–24.
[2] Shorvon S, Baulac M, Cross H, Trinka E, Walker M. The drug treatment of status epilepticus in Europe: consensus document from a workshop at the first London colloquium on Status Epilepticus. Epilepsia. 2008;49:1277–85.
[3] Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guidelines on the management of status epilepticus in adults. Eur J Neurol. 2010;17:348–55.
[4] Baddour E, Trewkbey A, Stauner N. Valproic acid-induced hyperammonemia: incidence, clinical significance, and treatment management. Ment Health Clin. 2018;8: 73–7.
[5] DeWolfe JL, Knowlton RC, Beasley MT, Cofield S, Faught E, Lindi NA. Hyperammonemia following intravenous valproate loading. Epilepsy Res. 2009; 85:65–71.
[6] Chicharro AV, de Marinis AJ, Kanner AM. The measurement of ammonia blood levels in patients taking valproic acid: looking for problems where they do not exist? Epilepsy Behav. 2007;11:361–6.
[7] Trinka E, Kalviainen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure. 2017;44:65–73.
[8] Ferenci P, Lockwood A, Mullen K, Tarter R, Weissborn K, Blei AT. Hepatic encephalopathy–definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716–21.
[9] Dharel N, Bajaj JS. Definition and nomenclature of hepatic encephalopathy. J Clin Exp Hepatol. 2015;5:337–41.
[10] Ulvin LB, Tauboll E, Olsen KB, Heuser K. Predictive performances of STESS and EMSE in a Norwegian adult status epilepticus cohort. Seizure. 2019;70:6–11.
[11] Murphy JV, Marquardt K. Asymptomatic hyperammonemia in patients receiving valproic acid. Arch Neurol. 1982;39:591–2.
[12] Lind J, Nordlund P. Intravenous use of valproic acid in status epilepticus is associated with high risk of hyperammonemia. Seizure. 2019;69:20–4.
[13] Chopra A, Kolla BP, Mansukhani MP, Netzel P, Frye MA. Valproate-induced hyperammonemic encephalopathy: an update on risk factors, clinical correlates and management. Gen Hosp Psychiatry. 2012;34:290–8.
[14] Segura-Bruna N, Rodriguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. Acta Neurol Scand. 2006;114:1–7.
[15] Verrotti A, Triota D, Morgese G, Ciarelli F. Valproate-induced hyperammonemic encephalopathy. Metab Brain Dis. 2002;17:367–73.
[16] Trinka E, Hofer J, Zerbs A, Brigo F. Efficacy and safety of intravenous valproate for status epilepticus: a systematic review. CNS Drugs. 2014;28:623–39.
[17] Lewis C, Deshpande A, Tesar GE, Dale R. Valproate-induced hyperammonemic encephalopathy: a brief review. Curr Med Res Opin. 2012;28:1039–42.