



# Intravenous use of valproic acid in status epilepticus is associated with high risk of hyperammonemia

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## ABSTRACT

**Purpose:** The aim of the study was to examine the frequency of hyperammonemia secondary to valproic acid treatment in status epilepticus and to describe the characteristics of the patients.

**Methods:** All patients with established status epilepticus during 2014 to 2016 at Ryhov County Hospital were identified in a retrospective case series. Clinical and laboratory findings were collected from electronic medical files and the Metavision database at the intensive care unit (ICU). Hyperammonemia was defined as a concentration of at least 50  $\mu\text{mol/L}$ .

**Results:** 11 of 40 patients developed hyperammonemia. These patients had a significantly longer stay at the ICU (12.6 vs 2.5 days) and at the hospital (22 vs 11 days). All patients with hyperammonemia were treated at the ICU and all received antibiotics. 12 patients were treated with intravenous valproic acid outside the ICU. Hyperammonemia was not related to Body Mass Index, time to initiation of therapy or laboratory abnormalities except anemia (Hemoglobin 104 vs 122 g/l). There was no difference in mortality between groups.

**Conclusion:** The risk of hyperammonemia is almost 40% in patients receiving intravenous valproic acid in the ICU setting. The underlying mechanisms are probably either individual susceptibility or high metabolic demands. A high vigilance should be recommended. These data require further research via prospective designs in which multiple variables are controlled to explore the effects of individual factors on treatment outcome.

## 1. Introduction

Status epilepticus (SE) is a neurological emergency with significant morbidity and mortality [1] and requires immediate treatment. In 2012 a committee from the Neurocritical Care Society published expert consensus guidelines [2], but there is a severe lack of double-blinded randomized controlled studies of the treatment of SE. Experts agree that benzodiazepines should be the agent of choice for emergent initial treatment [2]. Phenytoin, lorazepam and phenobarbital have been extensively used for this indication for many years, based largely on the evidence derived from the Veterans Affairs Cooperative Trial [3]. Valproate (VPA) has been available as an oral treatment in the U.S. since 1978 [4] and as an injectable formulation since 1993 [5]. VPA has become established as an effective broad-spectrum antiepileptic drug that is particularly useful for the management of generalized epilepsies, for which treatment alternatives are few. Intravenous VPA has been studied against intravenous phenytoin in two randomized studies. When given as first choice in status epilepticus, VPA aborted seizures in

66% and phenytoin in 42% [6], and in patients with benzodiazepine refractory status epilepticus it was as effective, but was easier to use and had fewer side effects [7]. In a systematic review published in 2014, the overall response rate in 848 patients with various forms of SE treated with intravenous VPA was 71% [5]. In another meta-analysis of the relative effectiveness of different antiepileptic drugs in the treatment of benzodiazepine-resistant convulsive status epilepticus the mean efficacy of VPA was found to be 76% [8].

Side effects of VPA have been regarded as few and limited to mainly dizziness, thrombocytopenia, and mild hypotension [5]. However, during the past few years increasing evidence has accumulated that the intake of valproic acid during pregnancy is associated with a significant risk of dose-dependent teratogenic effects and impaired postnatal cognitive development in children [9,10]. Hyperammonemia without hepatic dysfunction is an adverse effect that has been reported in the pediatric and adult populations at therapeutic VPA levels [11–13]. Hyperammonemic coma as a complication of VPA therapy was first reported by Barrueto and Hack in 2001. This patient had no other

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**Table 1**

Types of seizure at arrival to hospital and number of patients treated with valproic acid in each group.

Type of status epilepticus	Total number of patients	Number of patients treated with Valproic Acid	Percentage of patients treated with Valproic Acid
Convulsive status epilepticus	20	15	75
Focal status epilepticus	9	5	56
Non-convulsive status epilepticus	4	3	75
Secondary generalized tonic clonic	7	5	71

anticonvulsant therapy, metabolic abnormality, or hepatic dysfunction [14]. Other symptoms of hyperammonemic encephalopathy include focal neurologic deficits, cognitive slowing, violent outbursts, paranoid ideation, vomiting [4,15] and even status epilepticus [16]. The incidence of hyperammonemia during status epilepticus is not known but is expected to be high due to metabolic demands and polypharmacy.

The aim of the study was to examine the frequency of hyperammonemia in a retrospective case series of established status epilepticus and to describe the frequency and the characteristics of the patients.

## 2. Methods

The International League Against Epilepsy (ILAE) definition of Status Epilepticus (SE) was used requiring varying time limits depending on the type of seizures. For convulsive SE, 5 min or more of (i) continuous clinical and/or electrographic seizure activity or (ii) two or more discrete seizures between which there is incomplete recovery of consciousness [17]. For focal SE and absence SE the time was extended to 10 min. Patients with generalized SE were divided into two groups, convulsive SE (CSE) and secondary generalized SE if they had a period of focal seizures that developed into a CSE. Patients aged 18 years or older with a diagnosis of status epilepticus during 2014 to 2016 at Ryhov hospital were identified from the patient database at the intensive care unit (Metavision, iMDsoft, Wakefield, MA, U.S.A.) or the electronic medical files at the department of neurology (Cosmic, Cambio, Linköping, Sweden). A total of 40 individuals were identified. In patients with more than one episode of SE, only the first episode that had information about concentrations of VPA and ammonia was included. VPA and ammonia levels were analyzed on a clinical basis, and not according to a specified protocol. At the ICU, VPA was in most cases monitored daily and ammonia levels were tested if the patient had a prolonged status epilepticus or was not returning to full consciousness when sedation was ended. Data were collected from the medical files, Metavision and from laboratory reports at Ryhov Hospital (XRoS, Evry, Oslo, Norway). Hyperammonemia was arbitrarily defined as a plasma concentration of at least 50  $\mu\text{mol/L}$ .

Ergenyl® (Sanofi, Paris, France) was administered according to our local guidelines. For patients at the ICU and not previously on VPA treatment the loading dose was 20 mg/kg of Ergenyl® delivered over 5 min. All other patients received 15 mg/kg of 100 mg/ml. The bolus could be repeated if the patient was not on VPA treatment and was outside the ICU. If the status epilepticus persisted, the patient was transferred to the ICU, where continuous infusion with Ergenyl® 32 mg/ml at 1–2 mg/kg/h was delivered, and then adjusted according to clinical response and concentrations in plasma aiming at a concentration from 300 to 700  $\mu\text{mol/L}$ . Patients treated at the ICU were monitored with continuous EEG (cEEG).

### 2.1. Statistical analysis

Data was analyzed using Statistica Version 13.1, Dell Inc., Tulsa, OK, U.S.A. For comparison between two groups *t*-test was used. For ordinal data and data not normally distributed the Mann–Whitney U test was used. For nominal data Chi2 test was used. For groups with fewer than five respondents, the analysis was completed with Fisher's

exact test. Correlations were tested using Spearman rank order correlations. Differences were considered significant if *p*-values were < 0.05.

### 2.2. Ethical approval

The study was approved by the regional ethical committee in Linköping.

### 2.3. Abbreviations

cEEG = Continuous Electroencephalography  
 CI = Confidence Interval  
 CRRT = Continuous Renal Replacement Therapy  
 CSE = Convulsive Status Epilepticus  
 ICU = Intensive Care Unit  
 NCSE = Non-Convulsive Status Epilepticus  
 n.s. = Not Significant  
 SE = Status Epilepticus  
 sz = seizure  
 VPA = Valproic Acid

## 3. Results

We identified 40 patients with status epilepticus during the study period. The mean age was 62.8 years (range 20–88). Types of SE are described in Table 1. Patients with primary convulsive status epilepticus (CSE) arrived at hospital 59.3 min (95% CI 53.7–105) after start of seizure compared to 260 min in focal SE (95% CI 216–612), 761 min in non-convulsive SE (NCSE) (95% CI 578–6977) and 319 min from onset of focal sz in secondary generalized SE (95% CI 359–1228). At arrival patients were on continuous treatment with 0 to 15 different drugs (mean 6.5, 95% CI 5.3–7.7). Only 3 patients were treated with VPA before arrival. 2 patients were on fosphenytoin treatment, 2 clonazepam, 8 carbamazepine, 1 rufinamide and 1 on lacosamide at arrival. The 2 patients on fosphenytoin treatment were transferred to our hospital for cEEG due to refractory SE. The etiologies of SE were intracranial infarction or hemorrhage 13, medical disorders 5 (systemic infection 3, severe hyponatremia 1, Electro Convulsive Therapy [ECT] due to depression 1), CNS infection 4, CNS tumor 4, non-compliance to anti-epileptic drugs 3, idiopathic 3, cardiac arrest 3, misuse of alcohol or drugs 2 and autoimmune encephalitis in 1 case.

First line treatment was in 28 cases diazepam, 5 fosphenytoin, 4 VPA and in one case each midazolam, levetiracetam and propofol. Second line treatments was in 17 cases VPA, 10 levetiracetam, 7 fosphenytoin, 2 propofol, and in one case each midazolam, diazepam and lorazepam.

11 patients developed hyperammonemia. The characteristics of these patients compared to those who did not develop hyperammonemia are described in Table 2. There was no difference in laboratory tests at the time of peak ammonium levels except that the mean hemoglobin value was significantly lower in patients with hyperammonemia. There was a correlation between C-Reactive Protein (CRP) and decreasing hemoglobin ( $R = -0.43$ ,  $p < 0.05$ ) and concentration of ammonia ( $R = -0.47$ ,  $p < 0.05$ ), however there was no correlation between ammonia levels and hemoglobin.

The 28 patients exposed to VPA were analyzed separately. 13 were

**Table 2**

Characteristics of all 40 patients with and without hyperammonemia. Given values are number of patients or mean values (range lowest to highest value). P-values are considered significant if < 0.05. No corrections for multiple comparisons were made. sz = seizure. VPA = Valproic Acid. NH3 = ammonia.

	Hyperammonemia	No hyperammonemia	p-value
Number of patients	11	29	
Number treated at ICU	11	17	0.017
Age	55.9 (20–82)	65.5 (21–88)	0.12
Men	5	16	
Women	6	13	0.58
Body Weight (kg)	85 (57–119)	75 (46–121)	0.12
Height (cm)	172 (150–190)	170 (150–191)	0.68
Body Mass Index (BMI)	29 (22.8–43.4)	26 (15.8–37.0)	0.16
In from another ICU	3	1	
In from another clinic	1	4	
In from nursing home	1	11	
In from own home	5	12	
Status during care at own clinic	1	1	
Past history of epilepsy	3	16	
No previously epilepsy diagnosis	8	13	0.16
Cause: unknown	7	12	
Cause: postapoplectic	3	6	
Cause: other	1	4	
Sz: Generalized Tonic-Clonic	5	15	
Sz: Focal	1	8	
Sz: Non-convulsive	3	1	
Sz: Secondary Generalized	2	5	
Number of drugs on arrival	5.8 (0–15)	6.8 (0–15)	0.47
Minutes to first line treatment	493 (5–3543)	214 (5–1868)	0.28
Minutes to arrival at hospital	244 (0–2035)	199 (0–1562)	0.79
Minutes to second line treatment	2572 (142–7320)	469 (31–2094)	0.0001
Minutes from arrival to second line treatment	2040 (87–5670)	310 (3–1622)	0.0005
Days at ICU	12.6 (1.7–36)	2.5 (0.7–11)	0.0004
Hospital stay (days)	21.7 (2–60)	11 (1–46)	0.03
Loading dose of VPA (mg)	1512 (0–3000)	1423 (750–3400)	0.75
mg of VPA/kg	17.3 (0–35)	19.7 (12–40)	0.42
Maintenance dose of VPA (mg/h)	161.9 (65–374)	98.5 (0–192)	0.026
Maintenance dose of VPA (mg/h/kg)	1.89 (0.8–4.5)	1.40 (0.9–2.2)	0.11
Minutes from sz onset to first dose of VA	1933 (6–6415)	1263 (31–6353)	0.42
Mean of maximum concentration of VPA (µmol/L)	542 (81–816)	531 (182–839)	0.90
Minutes from arrival to first dose of VPA	877 (6–3706)	1083 (31–6384)	0.76
Minutes of VPA treatment to ammonia	5230 (966–12496)	2533 (463–7236)	0.16
Maximum concentration of ammonia (µmol/L)	94.3 (50–207)	31.7 (16–44)	0.0013
Hemoglobin (g/L)	104 (80–125)	122 (79–162)	0.013
LPK (x10e9/L)	10.4 (5.4–18.6)	10.6 (4.5–24)	0.91
TPK (x10e9/L)	193 (95–328)	255 (68–827)	0.17
Creatinine (µmol/L)	79 (30–199)	90 (39–404)	0.65
INR	1.3 (1.0–1.5)	1.6 (0.9–6.2)	0.62
C-Reactive Protein (mg/L)	47.6 (0–240)	44.5 (0–187)	0.87
ALP (µkat/L)	1.3 (0.7–3.3)	5.0 (0.6–66)	0.41
ALAT (µkat/L)	0.70 (0.29–1.39)	0.75 (0.19–3.05)	0.82
ASAT (µkat/L)	0.88 (0.39–2.10)	1.18 (0.26–5.44)	0.46
LD (µkat/L)	5.4 (2.4–8.3)	9.2 (3.8–14.6)	0.60
Discharged to other ICU	0	1	
Discharged to other clinic	4	6	
Discharged to nursing Home	1	8	
Discharged to home	2	6	
Diseased	4	8	0.70
Treated with meropenem	3	5	

**Table 2 (continued)**

	Hyperammonemia	No hyperammonemia	p-value
Not treated with meropenem	8	24	0.013
Treated with antibiotics	11	15	
Not treated with antibiotics	0	14	

men and 15 women. There was no difference in age (62.1 vs 64.7 years) between exposed and unexposed. All of the patients with hyperammonemia were treated with VPA and all were treated at the ICU in comparison to 10 of the 17 VPA exposed patients without hyperammonemia (p < 0.05). There was no difference in age, sex, body mass index or number of drugs at arrival. Only 3 patients were treated with VPA before the SE, and only one of them had an elevated concentration of ammonia (69 µmol/L after almost six days of intravenous treatment). 8/11 of the patients with hyperammonemia had no previous diagnosis of epilepsy compared to 5/17 without hyperammonemia (n.s.). There was no difference in time to first line treatment (493 min [95% CI -404-1390] vs. 147 [95% CI -83-377]), time to arrival at hospital (244 min [95% CI -272-761] vs 179 [95% CI -13-371]), but time to second line treatment was significantly longer both from start of seizure (2572 min [95% CI 950–4194] vs. 427 min [95% CI 134–720], p < 0.01) and from arrival at hospital (2040 min [95% CI 449–3630] vs. 247 min [95% CI 43–452], p < 0.01) for patients developing hyperammonemia. However, there was no difference in time from start of seizure (1933 [95% CI 412–3455] vs. 1263 [95% CI 245–2282] min) or arrival at hospital (877 [95% CI -113-1867] vs. 1083 [95% CI 158–2009] min) to initiation of treatment with VPA between groups. There was no difference in loading dose (17.3 [95% CI 11.1–24.5] vs. 19.7 [95% CI 16.5–22.9] mg/kg), maintenance dose (1.9 [95% CI 1.2–2.6] vs. 1.4 [95% CI 1.1–1.7] mg/kg/h) or maximum concentration (542 [95% CI 377–706] vs. 531 [95% CI 416–645] µmol/L) of VPA.

4 patients had peak levels of ammonia higher than 100 µmol/L. The time from start of VPA treatment to peak level was 17.4 to 144 h, in two cases within 36 h of treatment. These patients had a mean age of 43.8 (range 20–54) years. The youngest patient had no pharmacological treatment at arrival to hospital. Two of the patients had renal failure and three were treated with Continuous Renal Replacement Therapy (CRRT). In all of these patients VPA treatment was discontinued and there was no mortality in this group.

5 patients were treated with CRRT. 4 were exposed to VPA and had hyperammonemia (mean 125, range 79–207 µmol/L). In these 4 cases CRRT was initiated due to hyperammonemia in combination with loss of consciousness. In all these cases the CRRT treatment resulted in an improvement of consciousness, except the patient with the lowest ammonia levels, who deteriorated with cardiac failure and septicemia and died 3 days after initiation of CRRT. One of the patients treated with CRRT had recurrent hyperammonemia, which was found to be secondary to a portosystemic shunt.

#### 4. Discussion

Hyperammonemia in acute treatment of status epilepticus was reported in two cases in 2005 [18]. One previous prospective study has found a high rate of hyperammonemia, but all cases were considered to be transient and asymptomatic [19]. The risk for hyperammonemia for SE patients treated with VPA increased in patients treated at the intensive care unit (ICU). The risk was related to low hemoglobin levels and all patients were treated with antibiotics indicating that increasing metabolic demands in the liver during intensive care could be an explanation for this finding. However, the number of patients was too small to detect any other laboratory findings as markers of liver

dysfunction. There were no other useful risk factors for hyperammonemia.

Several actions provide the basis for the development of hyperammonemia that could lead to encephalopathy, but the most important mechanism is probably that VPA induces carnitine depletion. VPA is extensively metabolized in the liver by glucuronidation,  $\beta$ -oxidation in the mitochondria and  $\omega$ -oxidation. VPA crosses the membrane of liver mitochondria via the facilitation of carnitine. This pathway consists of several steps until it turns into valproyl-CoA in the mitochondrial matrix and is able to get into the  $\beta$ -oxidation process. However, long-term high-dose VPA therapy or acute VPA overdose is known to induce carnitine depletion and this could increase the  $\omega$ -oxidation route leading to higher concentration of the toxic metabolite 4-en-VPA. This is probably what happens during intensive care as well. All this could result in incorrect ammonia elimination through the urea cycle. Toxic metabolites of VPA inhibit carbamoyl phosphate synthetase, which catalyzes the conversion of ammonia to carbamoyl phosphate in the first step of the urea cycle deteriorating the situation, resulting in high levels of ammonia in blood [20].

Several significant factors may influence the chance of seizure cessation and final outcome of status epilepticus. These include variables such as the age of the patients, the etiology of the seizure, the choice of first line therapy, the duration of seizure before treatment was initiated, and dosage and rate of infusion of the drug [8]. This retrospective study was too small to fully analyze these variables, although they may have affected our results.

Surprisingly there was a significantly higher incidence of hyperammonemia in patients without previously diagnosed epilepsy. It was also found that 2 patients with ammonia levels above 100  $\mu\text{mol/L}$  developed hyperammonemia within 36 h, in one case without any previous medication. This indicates that some patients are prone to be bad metabolizers of VPA and most likely develop side effects and stop treatment with oral VPA.

There was no relation to loading dose, maintenance dose or maximum concentration of VPA and risk of hyperammonemia, which might be explained by rigorous monitoring of concentrations in blood and rapid changes in dosing if values were outside the therapeutic window. Infusion rates up to 30 mg/kg per min have been considered to be safe when given as loading dose [21,22], although all studies have not been performed in status epilepticus.

There was no obvious relation to other pharmaceutical therapies, but all patients with hyperammonemia were on antibiotics. Meropenem is widely used during intensive care in Sweden and known to interact with VPA [23], but was not more or less common in patients with hyperammonemia.

The evidence for CRRT-treatment of hyperammonemia secondary to VPA treatment in the literature is limited. It has been tried mainly in VPA poisoning and there are no firm guidelines about when to implement CRRT [24]. In our patients it was effective resulting in rapid improvement in most cases.

Compliance to local and national guidelines was poor probably due to the many therapies and treatment approaches available. In many cases first- and second-line treatments were delayed, which unfortunately is common in this patient group [25]. Hospital mortality was high, in part as patients with cardiac arrest was included. Mortality in other studies has ranged up to 60% [25].

How to treat status epilepticus still remains an enigma. Hopefully ongoing studies like The Established Status Epilepticus Trial which started enrollment in 2015 will give us answers [26], but for the time being we have to make decisions based on limited data and tolerance of the drugs. VPA has however some advantages. In addition to its high efficacy in acute situations, follow-up seizure freedom rates were also high, and the drug was well-tolerated, even with large doses (up to 100 mg/kg) and rates of infusion (up to 6 mg/kg/min). VPA administered intravenously reaches maximum concentrations within minutes and it is free of cardio-respiratory side effects which are important

advantages [8]. However, high doses of IV VPA are likely to cause hyperammonemia and in susceptible patients, it is likely that ammonia concentrations could rise to very high and potentially dangerous levels although data on this is limited [15]. This study indicates that ammonia levels should be monitored in an ICU setting or during prolonged intravenous treatment and stopped if levels increase. There are no established guidelines about the appropriate threshold to stop VPA treatment or to initiate dialysis.

This study has limitations. As it is retrospective, we were not able to identify all patients fulfilling the criteria of status epilepticus. Although we used the ILAE definition of SE [17,27] most patients had refractory or even super-refractory SE. However, all patients requiring intensive care for SE were identified from the intensive care unit database. The retrospective design also has the risk that the study was initiated due to clinical observations in the study period and could be a random cluster of events.

## 5. Conclusion

In conclusion, we found that the risk of hyperammonemia is alarmingly high in patients treated with intravenous VPA especially in the ICU setting causing prolonged hospitalization. A high vigilance should be recommended. These data require further research via prospective designs in future studies in which multiple variables are controlled to explore the effects of individual factors on treatment outcome.

## Declaration of interest

None.

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