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ORIGINAL RESEARCH ARTICLE

Acute Valproate-Induced Encephalopathy in Status Epilepticus: A Registry-Based Assessment

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Abstract

Background Valproate-induced encephalopathy (VIE) affects between 0.1% and 2.5% of patients under long-term epilepsy treatment. Its frequency and characteristics in adults with status epilepticus (SE) is, however, unknown.

Objective The aim of this study was to characterize the frequency and the clinico-biological characteristics of VIE in adult SE patients.

Methods We reviewed all patients included in our institutional SE registry who were treated for an SE episode between November 2021 and February 2023 and identified 39 patients who received valproate for their SE treatment. Acute VIE was defined by worsening of consciousness having led to the discontinuation of valproate, and improvement of consciousness within 96 hours after discontinuation of valproate during acute hospital treatment.

Results Patients had a mean valproate intravenous loading dose of 34.5 mg/kg and a mean maintenance dose of 15.3 mg/kg/d (1078 mg/d). Four out of 29 patients with measured ammonium had hyperammonemia. We identified four (10%) patients fulfilling acute VIE criteria. Median time from administration of valproate to the occurrence of VIE, and to resolution of VIE after cessation of valproate treatment, was 2 days for each. Three of the four VIE patients had no associated hyperammonemia. Patients who developed VIE more frequently had a history of liver disease ($p = 0.023$), and tended to be younger, but other clinical variables did not differ significantly from patients without VIE, including valproate loading or maintenance doses, SE cause, duration or severity, other concomitant antiseizure medications (none received topiramate, phenobarbital, or primidone).

Conclusion Pending larger studies, VIE in SE seems relatively frequent and difficult to foresee; clinical alertness to symptoms is mandatory, even without hyperammonemia, and valproate withdrawal should be considered in suspected cases.

Key Points

Acute valproate-induced encephalopathy (VIE) was found in 10% of our adult patients.

VIE did not seem to be associated with status epilepticus characteristics, hyperammonemia, valproate dosage or concomitant antiseizure medication.

As yet unrecognized patient characteristics could facilitate onset of VIE.

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1 Introduction

Status epilepticus (SE) is a neurological emergency requiring the rapid introduction of antiseizure medication (ASM) [1], typically organized in consecutive treatment lines, starting with a benzodiazepine and followed by intravenous ASM [2]. Valproate has been part of the therapeutic arsenal as a second-line agent for several decades. A recent randomized trial demonstrated similar efficacy of valproate compared with fosphenytoin or levetiracetam, with seizure control obtained in about half of the patients [3]. Currently, it remains one of the most widely used second-line agents, along with levetiracetam and lacosamide [4].

Valproate-induced encephalopathy (VIE) is a well-known complication affecting between 0.1% and 2.5% of patients under long-term epilepsy treatment [5, 6]. In several cases, it is the consequence of hyperammonemia, but non-hyperammonemic forms have also been described [7]. In its acute form, it is characterized by a disorder of consciousness, ranging from simple drowsiness to coma, which may be associated with psychiatric and behavioral manifestations and gastro-intestinal disturbances, generally appearing in the first few days following treatment introduction or modification [8]. The electroencephalogram (EEG) typically shows non-specific signs of encephalopathy, such as diffuse slowing of background activity and/or triphasic waves [9]. In its subacute-chronic form, the clinical presentation is rather characterized by cognitive symptoms and parkinsonism [8]. Risk factors associated with VIE are poorly understood, and some studies suggest a role for genetic polymorphisms and co-administration of other ASM, especially topiramate [5, 8]. There is conflicting evidence about the relationship between pre-existing liver dysfunction and valproate-induced encephalopathy [8].

Existing data concerning cases of acute encephalopathy induced by valproate during SE treatment are anecdotal [10, 11], even if it has been shown that hyperammonemia is a common finding in SE patients treated with intravenous valproate [11–13]. The aim of this study was to characterize the frequency and the clinico-biological characteristics of acute VIE in adult SE patients.

2 Methods

2.1 Study Population and Definitions

In this retrospective, observational safety analysis, we selected patients from our SE registry (SERCH, Status Epilepticus Registry at CHUV) included between November 2021 and February 2023 who received valproate for their SE episode. The registry comprises all adult (≥ 16 years) patients with SE hospitalized in our institution. We selected patients with SE according to the 2015 International League Against Epilepsy (ILAE) definition [1]. SE is defined as a generalized tonic-clonic seizure lasting > 5 min, a focal or absence seizure lasting > 10 min, or shorter, repetitive seizures without complete recovery between episodes. Nonconvulsive SE in coma (NCSEC) is defined by an EEG clearly suggestive of SE (i.e., repetitive rhythmic or periodic discharges with evolution in amplitude or frequency or continuous periodic lateralized or generalized epileptiform discharges) [14]. Refractory SE (RSE) was considered after the failure of first- and second-line ASM to control seizures [15]. Resolution of SE was determined as the moment of seizure termination, assessed clinically, and confirmed by EEG documentation. Subjects with SE in the context of cerebral anoxia are not part of the registry, due to marked difference in prognosis. SERCH follows our institutional regulations for clinical and research databases. All data stem from routine clinical management and were anonymized before analysis following the Swiss Human Research Act (given that anonymized data were used, there is no need for ethics commission approval or patient consent). Furthermore, as this is primarily a quality study of treatment practice, the Swiss Human Research Act does not require patient consents.

2.2 Patient Ascertainment

Among the included patients, we identified those who presented an acute VIE, defined by worsening of consciousness level (categorized as alert, confused, stuporous or comatose) having led to the discontinuation of valproate, and improvement of consciousness within 96 hours after valproate discontinuation during acute hospital treatment. Hyperammonemia or EEG alterations were not necessary for the definition. We excluded by chart review that concomitant modification of sedation or metabolic parameters could play a role in encephalopathy.

We considered clinical variables that were prospectively entered in the registry: demographics, occurrence of previous seizures, SE cause, worst seizure type, consciousness before treatment, STESS (Status Epilepticus Severity Score) [16], valproate loading dose/kg, valproate position in the treatment flow and mean maintenance doses, ASM and outcome at hospital discharge. We also retrieved history of liver disease or alcohol abuse, peak serum ammonia and valproate levels (typically reflecting residual values, as routinely taken in the morning before valproate administration) during the SE episode [15]. Hyperammonemia was defined at >50 µmol/L.

2.3 Statistical Analysis

For descriptive statistics, mean, standard deviation (SD), median and interquartile ranges (IQR) were used to describe continuous variables, and absolute values with percentages for categorial variables. For univariate comparisons, we used the Mann–Whitney *U* test for continuous variables (given the limited number in the VIE group) and the 2-sided Fisher's exact test for categorical variables. Statistical significance was set at $p < 0.05$. Given the exploratory nature of the study, no correction for multiple comparisons was applied. Calculations were performed using IBM SPSS version 28.0.1.1.

3 Results

3.1 Patient Characteristics

We identified 39 SE adults who received valproate during the study period. Patient and clinical characteristics, ASM data and laboratory results are summarized in Table 1.

The mean (SD) valproate intravenous loading dose was 34.5 (6.5) mg/kg and the mean (SD) maintenance dose was 15.3 (4.6) mg/kg/d or 1078 (313) mg/d. Two patients (not developing VIE) did not receive an intravenous valproate loading dose but continued previously administered valproate at unchanged doses. Mean peak valproate serum concentration (measured in 26 patients) was 47.2 mg/L, and 4/29 (14%) patients with measured ammonium had levels > 50 µmol/L (respectively 60, 61, and two at 71 µmol/L). None of the patients received concomitant phenobarbital, primidone, or topiramate.

3.2 Patients with Acute Valproate-Induced Encephalopathy (VIE)

We identified four patients who developed acute VIE, representing 10% of those receiving valproate. Comparison of patients with and without VIE is summarized in Table 2**.** Patients who developed VIE tended to be younger (not reaching significance), and more frequently had a history of liver disease (with former chronic hepatitis B or C infections; $p = 0.023$), while the other explored variables did not differ significantly. From what we could retrieve from the charts, no family history of liver disease, epilepsy, encephalopathy, or genetic predisposition (including mitochondrial) was found. Median time from administration of valproate to the occurrence of VIE was 2 days, and median time to resolution of VIE after cessation of valproate treatment was also 2 days.

4 Discussion

We found a frequency of acute VIE in SE-treated adults at 10%; besides a higher prevalence of history of hepatic disturbance in VIE and non-significant tendency to younger age, no clinical variable differed across the groups.

The higher prevalence of acute VIE in SE patients as compared with those with epilepsy (reported at 0.1 to 2.5% [5, 6]) may be the consequence of different underlying mechanisms of acute illness and ASM titration, subtending a vulnerability to this medication side effect. Besides, differing assessment criteria and definitions may also play a role. Nevertheless, these results suggest tolerability issues of valproate treatment in SE patients, as shown recently in epilepsy patients [17].

We did not find an association between VIE occurrence and SE characteristics (duration, severity as estimated with the STESS score, proportion of refractory cases), valproate dosage, or concomitant ASM medication. Surprisingly, VIE tended to occur in somewhat younger patients; this seems rather counterintuitive and might be related to the relatively small sample size. While an up to 10 times increased risk of VIE was described with topiramate [5], we could not confirm this, as none of our patients received it. Primidone and phenobarbital are also known risk factors of hyperammonemia and could facilitate VIE [18]. Again, none of the patients received those compounds. There was, however, an association between VIE and a history of liver disease, although there were no liver function test abnormalities at the time of the study. While existing data seem conflicting regarding the association between preexisting liver dysfunction and the risk of developing VIE [8], this was the only clinical variable showing a significant distribution asymmetry in our cohort.

Only one of four patients with VIE had hyperammonemia (defined as > 50 µmol/L), and 12% of patients who did not have VIE also had high ammonia concentration. This highlights the importance of looking for VIE even without concomitant hyperammonemia and demonstrates that this may not represent a reliable marker of VIE. As a matter of possible confounding, increase in serum ammonium has been described after a first unprovoked seizure in 48% of individuals not taking valproate [19]. Since ammonemia determination was performed only in 29 patients, finding an association between hyperammonemia and VIE occurrence in a small number of patients is difficult. Of note, all patients receiving valproate before the SE index episode did not develop VIE; while the numbers are small, preexposure to valproate may possibly represent a protecting factor.

While our cohort characteristics, with systematic consecutive patient ascertainment, are relatively similar to the

Table 1 Clinical characteristics of the 39 patients included in the study

Clinical and epidemiological data	
Female sex, *n* (%)	20 (51)
Age in years	65.4 (±19.5)
History of prior epilepsy, *n* (%)	23 (59)
Already on valproate therapy at SE start, *n* (%)	6 (15)
History of liver disease, *n* (%)	3 (8)
History of alcohol misuse, *n* (%)	3 (8)
SE characteristics	
Worst seizure type, *n* (%)	
Generalized convulsive	15 (38)
Generalized myoclonic/absence	2 (5)
Focal with/without impaired consciousness	20 (51)
Non convulsive SE with coma (NCSEC)	2 (5)
SE etiology[a], *n* (%)	
Structural[b]	25 (64)
Non-structural[b]	16 (41)
SE etiologic classification, *n* (%)	
Acute symptomatic	20 (51)
Remote symptomatic	4 (11)
Progressive symptomatic	13 (33)
Unknown	2 (5)
Level of consciousness before SE treatment, *n* (%)	
Alert	4 (10)
Confused	10 (26)
Somnolent	5 (13)
Stuporous	12 (31)
Comatose	8 (21)
SE duration in hours	74.5 (±61)
Refractory SE, *n* (%)	33 (85)
STESS	2.7 (±1.4)
Outcome at discharge, *n* (%)	
Return to clinical baseline	14 (36)
New handicap	13 (33)
Death	12 (31)
ASM	
Valproate intravenous loading dose in mg/kg ($n = 37$)	34.5 (±6.5)
Valproate maintenance dose in mg/kg/d	15.3 (±4.6)
Valproate position in the treatment flow	3.4 (±1.4)
Number of concomitant ASMs	4.7 (±1.6)
Valproate-induced encephalopathy, n (%)	4 (10%)
Laboratory values (serum)	
Peak valproate concentration in mg/L (reference: 50–100) ($n = 26$)	47.2 (±22.3)
Peak ammonia concentration in µmol/l (reference: <50) ($n = 29$)	38.0 (±14.5)
Ammonium > 50 µmol/L, *n* (%) ($n = 29$)	4 (14%)

Continuous variables are presented as mean (±SD)

ASM antiseizure medication, *n* number, *SE* status epilepticus, *STESS* status epilepticus severity score

[a]Several etiologies are possible for a single SE

[b]Structural causes encompass vascular/traumatic: 13 (33%) and neoplastic: 13 (33%). Non-structural causes encompass CNS infection/autoimmune: 4 (10%), systemic infection: 4 (10%), neurodegenerative: 2 (5%), metabolic, toxic, ASM withdrawals: 4 (10%) and unknown/idiopathic: 2 (5%)

Table 2 Comparison of patient's characteristics between patients who developed and didn't develop a valproate-induced encephalopathy

Variables	VIE ($n = 4$)	No VIE ($n = 35$)	p-Value
Clinical and epidemiological data			
Female, *n* (%)	3 (75%)	17 (49%)	0.605
Age in years	50.5 (24.5–68.3)	75.0 (63.0–77.0)	0.066
History of prior epilepsy, *n* (%)	3 (75%)	20 (57%)	0.631
Already on valproate therapy, *n* (%)	0 (0%)	6 (17%)	1.0
History of liver disease, *n* (%)	2 (50%)	1 (3%)	**0.023**
History of alcohol abuse, *n* (%)	0 (0%)	3 (8%)	1.0
SE characteristics			
SE duration in hours	64.5 (9.0–174.0)	60 (27.5–120.0)	0.806
Refractory SE, *n* (%)	4 (100%)	29 (83%)	1.0
STESS	2 (0–3)	3 (2–4)	0.102
SE structural etiology, *n* (%)	3 (75%)	22 (63%)	1.0
SE acute symptomatic etiology, *n* (%)	2 (50%)	18 (51%)	1.0
ASM			
Valproate intravenous loading dose in mg/kg ($n = 37$)	37.5 (31.3–42.3) ($n = 4$)	35 (30–40) ($n = 33$)	0.407
Valproate maintenance dose in mg/kg/d	13.0 (9.0–16.5)	14.3 (12.2–18.2)	0.268
Valproate position in the treatment flow	3 (2–5)	3 (2–5)	0.982
Number of concomitant ASMs	5 (3–7)	5 (4–6)	0.806
TPM concomitant treatment, *n* (%)	0 (0%)	0 (0%)	1.0
Laboratory values (serum)			
Peak valproate concentration in µmol/L (reference 50–100) ($n = 26$)	47.0 (40–54) ($n = 2$)	41.5 (33.3–58.8) ($n = 24$)	0.745
Peak ammonia concentration in µmol/L (normal: 0–50) ($n = 29$)	42.0 (35.0–64.5) ($n = 4$)	36.0 (26.0–44.0) ($n = 25$)	0.181
Ammonia >50 µmol/L, n (%) ($n = 29$)	1 (25%)	3 (12%)	0.467
VIE characteristics			
Time delay between valproate administration and VIE occurrence, in days	2 (1.5–6.5)		
Time delay between valproate discontinuation and VIE resolution, in days	2 (1.5–2)		

Bold numbers are significant in univariable analysis

Continuous variables are reported as the median (IQR) given the limited number of VIE cases. Mann–Whitney *U* test was used for continuous variables and Fisher's exact test for categorical or binary variables

ASM antiseizure medication, *IQR* interquartile range, *n* number, *SE* status epilepticus, *STESS* status epilepticus severity score, *TPM* topiramate, *VIE* valproate-induced encephalopathy

literature [20], this study should be interpreted in the light of some limitations. First, the sample size is relatively small with a relatively short observation period, which could result in an overestimation of VIE frequency, and limit analyses of associations. Second, our cohort shows frequent neoplastic SE etiology and RSE (reflecting the relatively severe profile of SE patients receiving valproate). Third, although based on prospectively collected data, it is retrospective, which prevents causality assessments. Some cases of VIE, especially mild forms, could have been missed, because VIE was not documented as such in the registry. Fourth, the lack of VIE biomarkers renders case ascertainment dependent on our clinical definition, which is broadly in line with the existing literature, where it is based essentially on consciousness alteration in patients under valproate, reversible after treatment cessation. There is no convincing criterion regarding EEG, which usually shows nonspecific signs of encephalopathy [8]. Fifth, ammonium serum concentration assessment was not systematic, and was performed without control values before the index SE episodes, and carnitine use was not assessed in the present ascertainment, as we do not routinely administer it [8]. Sixth, we determined total valproate level, not the free valproate fraction, the latter probably being better correlated with the onset of VIE, as only the free fraction crosses the blood–brain barrier [21]. Seventh, we did not find routine serum lactate levels in our charts.

5 Conclusion

To our best knowledge, this is the first study estimating the acute VIE incidence in SE patients. Like patients with epilepsy [17], valproate seems not so well tolerated in patients with SE. In this relatively small sample, VIE seems relatively frequent (10%), often occurred without hyperammonemia, and was possibly associated with preexisting liver disease. The otherwise similar profile between patients with and without VIE may suggest that as-yet unrecognized patient characteristics could facilitate its onset. Pending larger studies on this topic, clinical suspicion and an attempt at valproate withdrawal remain paramount in this context.

Declarations

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Conflicts of interest None of the authors has any conflict of interest to disclose.

Ethics approval We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Given that anonymized data were used, there was no need for ethics commission approval.

Consent to participate As this is primarily a quality study of treatment practice, and given that anonymized data were used, the Swiss Human Research Act does not require patient consent.

Consent for publication Not applicable.

Availability of data and material The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Author contributions VL: methodology (supporting), formal analysis, investigations (equal), writing—original draft preparation (leading). JN: writing—review and editing (equal). IB: writing—review and editing (equal). AOR: conceptualization, methodology (leading), investigations (equal), resources, supervision, writing—original draft preparation (supporting), writing—review and editing (equal). All authors wrote, edited, and significantly contributed to the final manuscript. All authors approved the final manuscript for submission.

References

1. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus-report of the ILAE task force on classification of status epilepticus. Epilepsia. 2015;56:1515–23.
2. Meierkord H, Boon P, Engelsen B, et al. European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol. 2010;17:348–55.
3. Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019;381:2103–13.
4. Beuchat I, Novy J, Rossetti AO. Newer antiepileptic drugs in status epilepticus: prescription trends and outcomes in comparison with traditional agents. CNS Drugs. 2017;31:327–34.
5. Noh Y, Kim DW, Chu K, et al. Topiramate increases the risk of valproic acid-induced encephalopathy. Epilepsia. 2013;54:1–4.
6. Lewis C, Tesar GE, Dale R. Valproate-induced hyperammonemic encephalopathy in general hospital patients with one or more psychiatric disorders. Psychosomatics. 2017;58:415–20.
7. Farooq O, Zunga PM, Dar MI, et al. Non-Hyperammonemic valproate encephalopathy. Ann Neurosci. 2014;21:76–9.
8. Wu J, Li J, Jing W, et al. Valproic acid-induced encephalopathy: a review of clinical features, risk factors, diagnosis, and treatment. Epilepsy Behav. 2021;120: 107967.
9. Segura-Bruna N, Rodriguez-Campello A, Puente V, et al. Valproate-induced hyperammonemic encephalopathy. Acta Neurol Scand. 2006;114:1–7.
10. Embacher N, Karner E, Wanschitz J, et al. Acute encephalopathy after intravenous administration of valproate in non-convulsive status epilepticus. Eur J Neurol. 2006;13:e5-6.
11. Smith KM, Britton JW, Hocker SE, et al. Hyperammonemia in patients with status epilepticus treated with or without valproic acid. Neurologist. 2021;26:80–2.
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. Habhab SF, Ulvin LB, Taubøll E, et al. Influence of valproate-induced hyperammonemia on treatment decision in an adult status epilepticus cohort. Epilepsy Behav. 2020;111: 107193.
14. Leitinger M, Trinka E, Gardella E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol. 2016;15:1054–62.
15. Vijiala S, André P, Buclin T, et al. Valproate in status epilepticus: correlation between loading dose, serum levels, and clinical response. Eur J Neurol. 2022;29:2607–11.
16. Rossetti AO, Logroscino G, Milligan TA, et al. Status epilepticus severity score (STESS): a tool to orient early treatment strategy. J Neurol. 2008;255:1561–6.
17. Willems LM, van der Goten M, von Podewils F, et al. Adverse event profiles of antiseizure medications and the impact of coadministration on drug tolerability in adults with epilepsy. CNS Drugs. 2023;37(6):531–44.
18. Fechner A, Hubert K, Jahnke K, et al. Treatment of refractory and superrefractory status epilepticus with topiramate: a cohort study of 106 patients and a review of the literature. Epilepsia. 2019;60(12):2448–58.
19. Sato K, Arai N, Omori A, et al. Hyperammonaemia and associated factors in unprovoked convulsive seizures: a cross-sectional study. Seizure. 2016;43:6–12.

20. Leitinger M, Trinka E, Giovannini G, et al. Epidemiology of status epilepticus in adults: a population-based study on incidence, causes, and outcomes. Epilepsia. 2019;60:53–62.

21. Fisch U, Baumann SM, Semmlack S, et al. Accuracy of calculated free valproate levels in adult patients with status epilepticus. Neurology. 2021;96(1):e102–10.