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ORIGINAL ARTICLE

Valproate in status epilepticus: Correlation between loading dose, serum levels, and clinical response

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Abstract

Background and purpose: Intravenous valproate (VPA) is an established treatment of status epilepticus (SE), but optimal loading dose was not fully assessed. We aimed at analyzing the correlation between VPA loading dose and subsequent plasma levels with clinical response in SE.

Methods: This was a retrospective study in one referral center of all consecutive VPA-naïve SE episodes treated with VPA between January 2013 and June 2019, in which total VPA trough plasma levels after intravenous loading dose were available. Response to VPA, defined as last antiseizure medication introduced before SE resolution (without the need for additional treatment), was correlated with VPA loading dose and trough level. Correlations were adjusted for other SE characteristics.

Results: Among 128 SE episodes, 53 (41%) responded to VPA. Median VPA loading dose was 25.2 mg/kg (range, 7–58 mg/kg). Loading doses and total plasma levels were not associated with the probability of response or mortality. Correcting for other possible confounders (number of previously tried treatment, demographics, SE severity) did not alter these findings. Only 3.8% of SE episodes that responded to VPA received >30 mg/kg.

Conclusions: A high loading dose (>30 mg/kg) is not associated with a greater response rate in patients with SE. Therefore, it seems to bring little benefit. If confirmed in further studies, a dosage of 25–30 mg/kg appears adequate in SE.

KEYWORDS
critical care, efficacy, pharmacokinetics, therapeutic drug monitoring, valproate

INTRODUCTION

Status epilepticus (SE) is a prolonged epileptic activity, secondary to the loss of mechanisms of seizure termination [1] and represents a neurologic emergency with sizeable morbidity and mortality [2]. Benzodiazepines constitute the first line of treatment, followed by intravenous (IV) antiseizure medications (ASMs) [3–5]. Valproate (VPA), phenytoin, and levetiracetam are the most used and studied IV ASMs in SE [6]. VPA is administered at varying loading doses, ranging between 15 and 45 mg/kg [7, 8]. Its use was recently compared to levetiracetam and fosphenytoin, with loading of 40 mg/kg in the ESETT trial [9]. However, high doses may not be innocuous, especially with risks of encephalopathy that can impact the patient outcome [7].

The relationship between VPA dosage in SE and its efficacy was not assessed. It is also not clear if VPA plasma levels within reference ranges established for epilepsy in an outpatient setting (between 50 and 100 mg/L [10]) are associated with a better response rate. Therefore, the ideal VPA loading dose is not established. In our center, a loading dose of 30 mg/kg is recommended for the treatment of SE [6].

Our study aimed at evaluating the current use of VPA in SE and at clarifying the potential association between VPA loading doses through plasma levels and SE response.

MATERIALS AND METHODS

We analyzed our previously described prospective SE registry [11], which was approved by our institutional review board and includes all consecutive adult patients with SE treated at the CHUV (Lausanne University Hospital). Inclusion is performed by two epileptologists (J.N. and A.O.R.) based on clinical evaluation and electroencephalography (EEG) (the latter being mandatory for nonconvulsive episodes). SE is defined as a single seizure that lasts >5 min in the case of generalized tonic–clonic seizures, more than 10 min in the case of focal seizures, or shorter consecutive seizures without complete recovery between the episodes [1]. Episodes occurring in patients younger than 16 years old or postcardiac arrest are excluded because of important differences in prognosis. Patients previously treated with VPA or incomplete data were excluded. Resolution of SE was determined as the moment of seizure cessation, assessed clinically and subsequently confirmed by EEG documentation, usually obtained within 24 h.

Patients' demographics, body weight, SE duration, and clinical characteristics, such as the presence of etiologies that may be potentially fatal [12, 13], were collected prospectively. The Status Epilepticus Severity Score (STESS) [14], a validated prognostic score, was prospectively calculated for every patient to account for the episode severity. The exact sequence and timing of administration of treatments, including loading VPA doses and delay of plasma samples, were collected. Response to VPA was considered if this was the last ASM introduced before SE resolution.

Total plasma concentrations of VPA (trough concentrations, usually assessed in the morning before the next VPA dosing) were measured by our hospital laboratory using enzyme immunoassay with a detection threshold of 12.5 mg/L. We considered plasma levels between 50 and 100 mg/L as complying with the long-established reference ranges [10].

Statistical analyses were performed on an anonymized data set with SPSS version 25 (IBM, Armonk, NY). The χ^2 or Fisher test and Mann-Whitney *U* test were used for univariable analyses, as needed. A binary stepwise backward logistic regression was used to adjust for predictors of response or mortality, namely STESS (including age), potentially fatal SE etiology, number of previously tried ASMs, and late (>1 h) treatment start with first-line agents.

RESULTS

We included 193 VPA-naïve SE episodes treated with VPA between January 2013 and June 2019 and whose VPA plasma level was measured. There was no recurrent SE episode. We excluded 65 episodes, 50 episodes because VPA serum levels were not collected directly after the loading dose (>24 h after the loading dose), and two because of incomplete data (unknown loading dose). Finally, 13 episodes were excluded because they withdrew their consent for the use of their data. Among the 128 SE episodes we analyzed, 53 (41%) responded to VPA. Demographics and SE characteristics in responders and nonresponders are compared in Table 1. There was no meaningful difference between both groups in terms of demographic characteristics.

Among the 128 episodes of SE analyzed, 48 (37.5%) were in generalized convulsive SE, 56 (43.8%) in focal SE, five (3.9%) in absence SE, 12 (8.5%) in non-convulsive SE in coma, and seven (5.5%) in unknown (whether focal or generalized SE). This stratification was included in the STESS score as a marker of SE severity for multivariable analyses.

VPA was given after a median of two lines of treatment (range, 0–5). The median loading dose was 1700 mg, respectively, 25.2 in mg/kg (range, 7–58 mg/kg). There was a small difference between responders and nonresponders in terms of loading dose, with nonresponders having received a slightly greater median weight-adjusted dose than responders (28 mg/kg vs. 23 mg/kg, $p = 0.021$). This difference would not remain significant after correcting for multiple testing. Distribution of loading doses and VPA plasma levels according to response are shown in Figures 1 and 2. Only 3.8% of SE episodes responding to VPA received >30 mg/kg.

There was a correlation between serum levels and loading doses related to body weight ($p = 0.006$, Spearman test). Of note, one episode fulfilled the criteria for response to VPA and had plasma levels below the levels of detection (<12.5 mg/L). No identifiable factors were found when considering all potential predictors of VPA loading dose (age, gender, STESS score, number of previous treatment lines, refractory SE, potentially deadly etiology, late treatment).

In a multivariable analysis including all potential predictors of response (VPA loading dose, number of previous treatment lines, VPA level, late treatment, STESS score, potentially fatal etiology), a greater number of previous treatment lines (odds ratio [OR] = 1.47, 95% confidence interval [CI] = 1.04–2.08, $p = 0.028$) and a lesser VPA loading dose (OR for an increasing dose [milligrams per kilogram] = 0.93, 95% CI = 0.88–0.98, $p = 0.008$) were independent predictors for a positive response to VPA. We then performed a sensitivity analysis considering 13 additional SE episodes (the number of episodes in which patients refused the use of their data) in which we set parameters to challenge our findings. Therefore, we considered that these fictional SE episodes would have received the greatest VPA loading dose of the range found in the study early in the treatment course and would have all responded to the treatment. This did not find that VPA loading dose or number of previous treatment lines were associated with response to the treatment.

TABLE 1 Details of SE episodes according to their response to VPA

	All, $n = 128$	Responders, $n = 53$	Nonresponders, $n = 75$	p	Test used
Age, years, median (range)	66 (17–93)	66 (19–93)	66 (17–91)	0.61	Mann-Whitney U
Female sex (%)	55 (43)	18 (34)	37 (49.3)	0.84	χ^2
STESS score, median (range)	3 (0–6)	3 (0–5)	3 (0–6)	0.64	Mann-Whitney U
Potential deadly etiology (%)	64 (50)	22 (44)	42 (56)	0.11	χ^2
Previous lines of treatment, median (range)	2 (0–5)	2 (0–5)	2 (0–4)	0.19	Mann-Whitney U
Refractory SE (%)	72 (58.6)	32 (60.4)	40 (53)	0.43	χ^2
Loading dose, mg, median (range)	1700 (500–4080)	1600 (500–2700)	1800 (900–4080)	0.37	Mann-Whitney U
Loading, mg/kg, median (range)	25.2 (6.75–57.7)	23 (6.75–34.78)	28 (11.76–57.69)	0.021	Mann-Whitney U
Dose ≥30 mg/kg (%)	35 (27.3)	9 (17)	26 (34.7)	0.027	χ^2
Valproic acid level, median (range)	49.5 (<12–112)	50 (<12–112)	47 (15–99)	0.54	Mann-Whitney U
Proportion of VPA level in the reference range (%)	62 (44)	26 (39.4)	36 (48)	0.91	χ^2
Late treatment, >1 h (%)	75 (58.6)	27 (50.9)	48 (64)	0.14	χ^2
Death (%)	19 (14.8)	5 (9.4)	14 (18.7)	0.15	χ^2

Abbreviations: SE, status epilepticus; STESS, Status Epilepticus Severity Score; VPA, valproate.

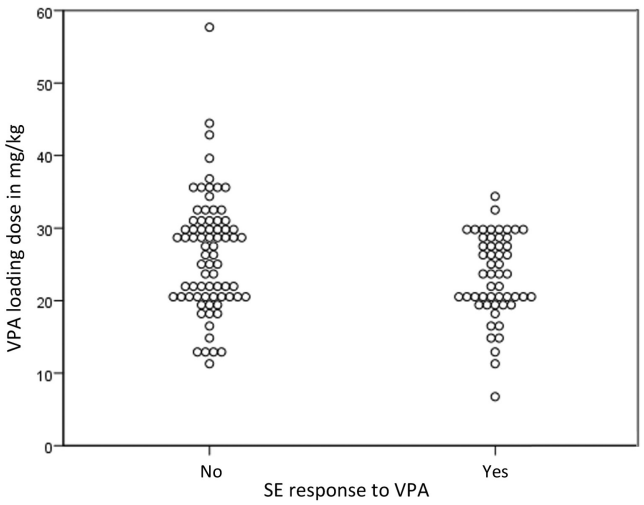

FIGURE 1 Distribution of VPA loading doses according to the response to VPA. The difference reached significance (median: 28 mg/kg in nonresponders vs. 23 mg/kg, $p = 0.021$, Mann-Whitney U test), but is not significant when correcting for multiple testing (Bonferroni test). Only 3.8% of SE episodes that responded to VPA received >30 mg/kg. SE, status epilepticus; VPA, valproate

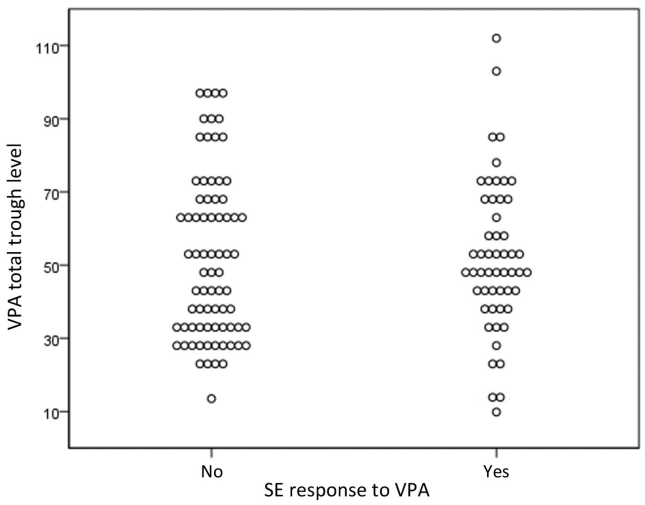

FIGURE 2 Distribution of VPA total trough levels according to the response to VPA. There was no significant difference (median: 47 mg/L in nonresponders versus 50 mg/L, $p = 0.021$, Mann-Whitney U test). SE, status epilepticus; VPA, valproate

There was no significant difference of distribution of loading doses ($p = 0.413$, Mann-Whitney U test) or VPA plasma levels ($p = 0.949$, Mann-Whitney U test) according to mortality. In a multivariable analysis, older age was the only predictor of mortality (OR per year = 1.06, 95% CI = 1.01–1.1, $p = 0.005$).

Among the 128 episodes, 94 (56.48%) received benzodiazepines as first-line treatment and 34 (43.52%) received a nonbenzodiazepine ASM as first-line treatment. Among the nonbenzodiazepines ASM first-line treatment, levetiracetam was administered in half of these (17 episodes [overall 21.76%]), and 11 received VPA (14.08%). This heterogeneity is explained by the variety of intervening physicians and SE characteristics. The subgroup of patients who received VPA as the first-line treatment was too small for further analysis, and its response rate to VPA was relatively low (2/11). In the 72 (56.2%) episodes that received more than two lines of treatment (refractory SE), only lesser loading dose (<30 mg/kg) ($p = 0.024$) and the absence of

potentially fatal etiology ($p = 0.043$) were associated with response to VPA. When performing a multivariable analysis, only lesser loading dose (considered as a continuous variable) was independently associated with response to VPA (OR = 0.92, 95% CI = 0.87–0.99, $p = 0.024$).

DISCUSSION

Our study did not find a benefit of increasing VPA loading dose in SE >30 mg/kg as well as targeting VPA total plasma level in the 50–100 mg/L reference range. Other established predictors of response to SE do not seem to confound these findings. Results of the multivariable analysis were somewhat surprising, suggesting that later use of VPA (not as the first line?) and a lesser loading dose was associated with greater response rate to VPA when adjusting for SE severity. These results were obtained after excluding patients who refused to allow their data to be used; when challenging those findings with a sensitivity analysis, these findings were not significant. Therefore, it is not clear if these findings really reflect on a better efficacy at a lower dose later in the treatment sequence or they represent artifacts of an incomplete cohort. This hypothesis should be evaluated in a larger prospective study.

There is no controlled trial assessing different dosages of VPA in SE and therefore no clear evidence about how much VPA should be administered in that setting. For instance, VPA loading dose in the recent ESETT trial evolved overtime from 30 mg/kg in the planning to 40 mg/kg in the trial [15]. Using the same design as this study, we previously found similar results with levetiracetam and lacosamide [16, 17], showing that increasing loading doses as much as the tolerability allows does not bring a tangible benefit in efficacy. However, this contrasts with brivaracetam [18], which was mostly administered using the maximal intravenous maintenance dose that was not sufficient enough to quickly reach efficacious levels. There is also evidence in the ESETT trial [19] that overweight patients (thus underdosed with doses capped for a weight of 75 kg at 3000 mg) had similar response rates as patients who received 40 mg/kg. The authors concluded that doses of 40 mg/kg may have led to drug concentrations greater than those needed for the treatment of SE. Varying VPA metabolism was also considered as a potential confounder, but as shown in this study, interindividual pharmacokinetic variability did not explain the response to the treatment.

Similar findings are not restricted to the treatment of SE. There is supporting evidence more widely in the treatment of epilepsy [20–25] that above a given ASM dose/level, benefits are limited in terms of efficacy. Therefore, using lesser loading doses might help improve the treatment tolerability, especially when a polytherapy is needed. In the particular case of VPA, minimizing dosage in SE might prevent occurrence of adverse events such as VPA encephalopathy. There are suggestions that the risk of encephalopathy is correlated with VPA maintenance dosage [7].

The ToSEE study [26], started in February 2021 in Germany, aims to generate evidence for the treatment of the benzodiazepine-resistant (established) status epilepticus in the elderly comparing VPA to levetiracetam, its results are expected in 4 years.

This study has several limitations. First, the retrospective identification of patients could lead to an inclusion bias. However, we collected plasma samples for the majority of episodes treated with VPA during the study period (only 25% did not have VPA available plasma levels). Second, the possible unequal distribution of outcome predictors between responders and nonresponders due to the selected nature of the sample may have masked an effect of VPA loading dose. We adjusted the analysis for most potential confounding variables (SE severity, potentially fatal etiology, number of previously failed treatments, late treatment), using multivariable analyses. Third, the SE response definition (last drug added that terminates SE) is admittedly simplistic and does not take into account potential synergistic effects of the ASMs administered or the natural evolution of the SE episode; one patient in our study responded to VPA with a level below detection levels. The definition we used remains the only applicable in clinical practice despite its limitations; SE response was judged clinically without continuous EEG, but this corresponds to clinical practice in many centers because 24h EEG monitoring is not available in many centers. Finally, the total plasma concentrations of VPA correspond mostly to the protein bound fraction, thus potentially not accounting for the biologically active free proportion. The proportion of binding can vary depending on its concentration as well as on concomitant medication (typically phenytoin). Albumin or overall serum protein level (not available in our study) can also help approximating VPA free levels. Further study measuring free VPA levels are needed to explore if this more relevant marker could help in assessing the response to VPA.

In conclusion, VPA loading doses >30 mg/kg are not associated with better response rates in patients with SE. Similarly, reaching total VPA plasma level reference range is not associated with a better prognosis. VPA loading doses of 30 mg/kg seem sufficient to control SE in VPA responsive episodes if confirmed in other cohorts.

AUTHOR CONTRIBUTIONS

Pascal Andre: Validation (equal); visualization (equal); writing – review and editing (equal). **Thierry Buclin:** Validation (equal); visualization (equal); writing – review and editing (equal). **Laurent Arthur Decosterd:** Validation (equal); visualization (equal); writing – review and editing (equal). **Andrea O. Rossetti:** Conceptualization (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

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