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Factors associated with subtherapeutic levels of valproic acid in hospitalized patients with epilepsy

A retrospective cohort study

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Abstract

Valproic acid (VPA) is a commonly used anti-seizure medication, owing to its efficacy and cost-effectiveness. However, maintaining appropriate serum levels is crucial due to the narrow therapeutic window, as subtherapeutic levels can lead to treatment failure or adverse outcomes. This study aimed to identify the factors associated with subtherapeutic serum levels of valproic acid in patients undergoing treatment. This retrospective cohort study was performed at a tertiary care hospital and involved inpatients aged ≥ 18 years who were receiving valproic acid for epilepsy treatment. Data were obtained through chart reviews and a Therapeutic Drug Monitoring database. Subtherapeutic VPA levels were defined as < 50 mg/L. Logistic regression was used to identify risk factors for subtherapeutic levels. Of the 152 patients, 96 (63.2%) had subtherapeutic VPA levels (<50 mg/L). Males were more likely than females to have subtherapeutic levels (OR 2.45, 95% CI: 1.15–5.22; $P = .02$). Previous use of phenytoin significantly increased the risk of subtherapeutic VPA levels (OR 2.58, 95% CI: 1.16–5.71; $P = .02$). VPA administration by syrup and doses below 15 mg/kg/day were associated with subtherapeutic levels (OR 3.28 and 2.34, respectively). Additionally, co-medications, such as topiramate and meropenem, also increased this risk (OR 5.09 and 4.64, respectively). This study identified several factors significantly associated with subtherapeutic levels of valproic acid, including males, prior phenytoin use, co-medications, such as topiramate and meropenem, and lower VPA dosages. These findings underscore the importance of careful monitoring and individualized treatment plans to maintain therapeutic VPA levels in clinical practice. Further research is needed to explore the clinical implications and to develop strategies to minimize the risk of subtherapeutic levels in patients receiving VPA.

Abbreviations: ASM = anti-seizure medication, TDM = therapeutic drug monitoring, UGT = UDP-glucuronosyltransferase, VPA = valproic acid.

Keywords: subtherapeutic, therapeutic drug monitoring (TDM), valproic acid

1. Introduction

Valproic acid (VPA) is one of the most widely used anti-seizure medications (ASMs) for the treatment of various types of seizures.[1] It is also used in the treatment of bipolar disorder, schizoaffective disorders, neuropathic pain, and migraine prevention.[2] However, the monitoring and measurement of VPA levels are crucial due to its narrow therapeutic range. The therapeutic levels for treating epilepsy are 50–100 and 50–125 mg/L when used as mood stabilizers.[3] If the concentration exceeds these levels, it may lead to toxicity, whereas concentrations below these levels may render treatment ineffective. Given the narrow therapeutic range of VPA, therapeutic drug monitoring (TDM) should be implemented to ensure its efficacy and safety in epilepsy treatment. In Thailand, pharmacists can utilize interpreted drug-level information by advising physicians to monitor drug levels and adjust individual dosage regimens accordingly.[4] To our knowledge, multiple pharmacokinetic mechanisms affect VPA levels, such as drug interactions, medical comorbidities, genetic polymorphisms, and perhaps formulations and rarely autoinduction.[5] The interpretation of VPA levels is essential to consider factors influencing drug levels because of the unpredictable relationship between dose and VPA levels.[6]

VPA is highly protein-bound and undergoes extensive liver metabolism, including glucuronidation and cytochrome P450 pathways. It inhibits UGT enzymes (UGT1A4 and UGT2B7) as well as CYP2C9, and to a lesser extent, CYP2C19 and CYP3A4, leading to several drug-drug interactions.[7] Co-administration of enzyme-inducing ASMs such as carbamazepine, phenytoin, primidone, and phenobarbital significantly reduce serum VPA concentrations by 50% to 75%,[8] which can compromise

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seizure control if the dosage is not adjusted. Additionally, interactions with non-ASMs, such as carbapenem antibiotics[9] and oral contraceptives,[10] also decrease serum VPA concentrations, necessitating careful monitoring of VPA levels to ensure therapeutic efficacy.

In previous studies, the serum concentration in hospitalized patients was often lower than the standard concentration and fluctuated in blood concentration with valproate sodium tablets.[11] Compared to the therapeutic range, low levels of VPA can reduce seizure control.[12,13] Factors that lower VPA levels should be determined for optimal clinical outcomes, especially in patients with multiple concomitant medications and the complexity of care.

Therefore, our study aimed to investigate the factors associated with subtherapeutic levels of VPA and to examine the relationship between these factors and subtherapeutic levels of VPA in inpatients with epilepsy.

2. Methods

2.1. Study design

This study was designed as a retrospective cohort study, utilizing chart reviews and data from the TDM database to analyze hospitalized patients receiving VPA for epilepsy treatment.

2.2. Setting and data source

Data were extracted from inpatient medical records and the TDM database at Sunpasitthiprasong Hospital, a tertiary care facility and the largest hospital in the province, with a capacity of 1188 beds as of 2024. The study included patients admitted between January 1, 2017, and December 31, 2019. This hospital serves as a referral center for surrounding community hospitals, providing comprehensive care for epilepsy patients, including TDM services. Eligible patients met the study's inclusion criteria: both those with subtherapeutic VPA levels below 50 mg/L and those with therapeutic levels between 50 and 100 mg/L. Patients were followed up from admission to discharge, and if multiple TDM measurements were available, the latest value was used for classification. Patients with supratherapeutic VPA levels (>100 mg/L) and those with incomplete sampling or clinical data were excluded.

2.3. Ethical statement

This study was approved by the ethics committee of Sunprasitthiprasong Hospital, Ubon Ratchathani, Thailand (no. 043/63 R).

2.4. Participants

The eligibility criteria for the study were as follows: male or female patients aged 18 years or older diagnosed with epilepsy, patients receiving VPA treatment, patients admitted to the inpatient department of a tertiary care hospital, and patients with documented laboratory test results for VPA levels during their treatment. Patients with supratherapeutic VPA levels (>100 mg/L) or incomplete sampling data were excluded from this study. Participants were selected from inpatient admissions and followed from admission to discharge. Data were collected using a form specifically designed by the researchers to capture relevant clinical and laboratory information throughout patient hospitalization.

This study used a retrospective data collection method, knowing the exact population size of 220 patients who underwent blood testing for VPA levels during the study period. Sample size determination used Yamane's formula,[14] appropriate for known populations, with a statistical significance level set at 0.05. Therefore, a minimum sample size of 142 patients were used in this study.

2.5. VPA level assessment

Blood samples for VPA levels were collected from inpatients, and only total (bound) VPA levels were measured. To ensure accuracy, VPA levels were measured as trough levels, defined as samples taken within 30 minutes before the next dose, adhering to standard practice. Samples collected more than 1 hour before the next dose were excluded to maintain consistency in trough level measurements.

2.6. Variables

The primary outcome was VPA level, categorized as therapeutic (50–100 mg/L) or subtherapeutic (<50 mg/L). Exposures included the formulations and dosages of VPA administered, which were classified into 4 categories based on the route and form of administration: syrup, sustained release tablets, IV continuous drip, and IV bolus. The daily dose of VPA was initially recorded as a continuous variable in mg/kg/day and was subsequently categorized into 4 distinct groups: <15 mg/kg/day, 15 to 30 mg/kg/day, 31 to 45 mg/kg/day, and > 45 mg/kg/day, to assess its impact on achieving therapeutic serum levels. Predictors included demographic information (age and gender), comorbidities, and medications received prior to hospitalization. Potential confounders considered were other medications affecting VPA metabolism such as enzyme inducers or inhibitors. Blood level orders for TDM were used to determine VPA levels.

To minimize potential sources of bias, we established strict inclusion and exclusion criteria to ensure a homogenous study population. VPA levels were consistently measured as trough levels to reduce variability due to timing differences in the blood sampling. Samples collected more than 1 hour before the next dose were excluded to prevent the inaccurate classification of VPA levels. Data collection forms were standardized and designed by the researchers to ensure uniform data capture across all participants. Efforts were made to control for confounding factors, such as concurrent medications and comorbid conditions by recording these variables and including them in the statistical analysis. Patients with missing data were excluded from the study.

2.7. Statistical analysis

Continuous variables, such as age, were analyzed using the *t* test, whereas categorical variables, such as comorbidities and prior medication use, were analyzed using the chi-square or Fisher's exact tests, as appropriate. A multivariate logistic regression analysis was performed to identify predictors of subtherapeutic VPA levels, including variables with a *P* value of <0.1 in the univariate analysis to adjust for potential confounders. Statistical significance was defined as a 2-sided *P*-value < 0.05. All analyses were conducted using the STATA version 14 software.

3. Results

3.1. Baseline characteristics

This study included 155 patients with epilepsy who received VPA and underwent TDM. Three patients were excluded owing to incorrect sampling times, leaving 152 patients in the final analysis, with a mean duration of 22.72 days and a median of 7 days. The follow-up period ranged from a minimum of 1 day to a maximum of 418 days, reflecting substantial variability among patients.

The baseline characteristics of patients with VPA levels were categorized into 2 groups: those with subtherapeutic levels (VPA < 50 mg/L) and those with therapeutic or higher levels (VPA ≥ 50 mg/L), as shown in Table 1. Of these, 96 (63.16%) had VPA levels below the therapeutic range (<50 mg/L). A higher proportion of males was observed in the subtherapeutic group (67.7%) compared to the therapeutic group (48.2%; $P = .02$).

Regarding medication factors, we found that previously phenytoin administration was significantly associated with subtherapeutic VPA levels ($P = .01$). Topiramate and Meropenem also showed significant associations with P values of .01 and .05, respectively. Although imipenem demonstrated statistical significance ($P = .01$), it was observed only in the subtherapeutic group and not in the therapeutic group. VPA syrup use was higher in the subtherapeutic group than in the therapeutic group (11.5% vs 3.6%, $P = .02$). For VPA Dosage We found that lower doses of VPA (<15 mg/kg/day) were associated with subtherapeutic levels ($P = .04$).

Table 1

Baseline characteristics (N = 152).

Parameters	Serum VPA level < 50 mg/dL (N = 96)	Serum VPA level ≥ 50 mg/dL (N = 56)	*P* value
Demographics			
Gender, n (%)			.02
Male	65 (67.7)	27 (48.2)	
Female	31 (32.3)	29 (51.8)	
Age (yr), mean ± SD	50.95 ± 18.4	53.33 ± 18.9	.21
Weight (kg), mean ± SD	57.33 ± 10.9	56.41 ± 10.9	.69
Comorbidities, n (%)			
Hepatic impairment	3 (3.1)	1 (1.8)	.62
Cardiovascular disease	17 (17.1)	12 (21.4)	.57
Endocrine disease	26 (27.1)	9 (16.7)	.12
Hematological disease	7 (7.3)	2 (3.6)	.35
Neurologic disease	27 (28.1)	14 (25.0)	.35
Infectious disease	14 (14.6)	8 (14.3)	.96
Previous medication, n (%)			
No	18 (18.8)	14 (25.0)	.27
Phenytoin	46 (47.9)	13 (23.2)	.01
Levetiracetam	11 (11.5)	9 (16.1)	.39
Phenobarbital	9 (9.4)	6 (10.7)	.68
Carbamazepine	1 (1.0)	2 (3.6)	.49
Antihypertensive drugs	20 (20.8)	9 (16.1)	.45
Lipid-lowering drugs	27 (28.1)	11 (19.6)	.27
Anticoagulants	4 (4.2)	5 (8.9)	.50
Antiplatelets	19 (19.8)	9 (16.1)	.54
Others	44 (45.8)	22 (39.3)	.31
VPA administration, n (%)			
Syrup	11 (11.5)	2 (3.6)	.02
Sustained release	52 (54.2)	30 (53.6)	.73
IV continuous drip	20 (20.8)	16 (28.6)	.19
IV bolus	13 (13.5)	8 (14.3)	.63
VPA(mg/kg/day), n (%)			
<15	27 (28.1)	8 (14.3)	.04
15–30	42 (43.8)	39 (69.7)	.10
31–45	13 (13.5)	8 (14.3)	.73
>45	4 (4.2)	1 (1.8)	.35
Co-medications, n (%)			
ASMs			
Phenytoin	67 (69.8)	33 (58.9)	.17
Levetiracetam	14 (14.6)	12 (21.4)	.31
Phenobarbital	7 (7.3)	7 (12.5)	.38
Carbamazepine	1 (1.0)	1 (1.8)	.74
Topiramate	2 (2.1)	6 (10.7)	.02
Others	21 (21.9)	12 (21.4)	.76
Non-ASMs			
Meropenem	13 (13.5)	2 (3.6)	.05
Imipenem	11 (11.5)	0 (0)	.01
Ertapenem	1 (1.0)	0 (0)	.38
Others	2 (2.1)	1 (1.8)	.93
Serum albumin, n (%)			
Normal (3.8–4.3)	37 (38.5)	25 (44.6)	.55
Hypoalbuminemia (<3.8)	39 (40.6)	21 (37.5)	
Platelet, n (%)			
140,000–400,000	70 (72.9)	40 (71.4)	.49
<140,000	14 (14.6)	12 (21.4)	
Liver function test, n (%)			
Normal	17 (17.7)	13 (23.2)	.71
Abnormal	39 (40.6)	24 (42.9)	

ASM = anti-seizure medication, VPA = valproic acid.

Other parameters, including comorbidities, co-medications, serum albumin levels, platelet counts, and liver function test results, were not significantly different between groups.

3.2. Determinants of subtherapeutic VPA levels

Factors associated with subtherapeutic VPA levels Male patients were more likely to have subtherapeutic VPA levels (OR 2.45, 95% CI: 1.15–5.22; $P = .02$). Previous phenytoin use increased the risk (OR 2.58, 95% CI: 1.16–5.71, $P = .02$). VPA administration by syrup increased the risk (OR 3.28, 95% CI: 1.12–9.68, $P = .03$). A VPA dose of < 15 mg/kg/day was also correlated with subtherapeutic levels (OR 2.34, $P = .04$). Co-medications, including topiramate and meropenem, were associated with higher subtherapeutic risks (OR 6.21, $P = .02$; and OR 4.27, $P = .04$, respectively). Imipenem could not be used in the logistic regression analysis because it was observed only in the subtherapeutic group (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/N880 which presents the results of univariate and multivariate logistic regression models of all variables). These findings suggest that specific demographics, medication prior hospitalization, co-medications, and dosage regimens significantly influenced VPA levels (Table 2).

4. Discussions

The findings of this study highlight several critical factors that influence subtherapeutic VPA levels in inpatients with epilepsy. Male patients were found to have a significantly increased risk of subtherapeutic VPA levels, suggesting potential gender-based pharmacokinetic differences. VPA is primarily metabolized through 3 pathways: glucuronidation, β-oxidation, and CYP450 enzymes. Previous studies[15,16] have shown that females tend to have lower UDP-glucuronosyltransferase (UGT) activity, which may lead to reduced VPA clearance in women, potentially resulting in higher VPA levels compared to men. However, in contrast to a previous study on Chinese children,[17] gender was not related to VPA concentration or efficacy.

In this study, we found that previous phenytoin uses and co-medications such as topiramate and meropenem underscored the importance of considering drug interactions in therapeutic monitoring. For phenytoin and topiramate, a population-based pharmacokinetic–pharmacodynamic model[18] found that age, seizure locus, SCN1A rs3812718 polymorphism, and co-administration of carbamazepine, clonazepam, phenytoin, and topiramate influenced VPA levels in patients with epilepsy, thereby reducing seizure frequency. As observed in the routine therapeutic drug monitoring data in Japan,[19] concomitant ASMs such as phenobarbital, carbamazepine, and phenytoin can lower serum VPA levels, whereas zonisamide does not significantly affect these levels in patients with epilepsy. Enzyme-inducing ASMs such as phenytoin, phenobarbital, and carbamazepine are known to reduce the serum concentration of VPA. However, in our study, the number of patients treated with phenobarbital and carbamazepine was small; therefore, there was no significant difference between the 2 groups.

Additionally, the use of VPA syrup is likely associated with an increased risk of subtherapeutic levels, despite VPA having high absorption and 100% bioavailability.[20] Previous study[21] has shown that the bioavailability of tablet and syrup formulations is not significantly different. Due to the limited number of adult patients using VPA syrup, particularly in inpatient settings, our study found it is often administered via a nasogastric tube. Some studies suggest potential interactions between protein supplements and VPA, recommending that they should be administered separately.[22]

VPA dosages below 15 mg/kg/day were associated with subtherapeutic levels, emphasizing the need for appropriate dosing strategies. These findings highlight the need to develop appropriate dosing strategies. We used a cutoff of 15 mg/kg/day, based on the usual starting dosage for adult patients with epilepsy, with a maximum VPA dosage of 60 mg/kg/day.[23] Although there is a strong correlation between the dose and level of VPA,[18] VPA exhibits nonlinear pharmacokinetics due to concentration-dependent protein binding,[8] meaning that increases in dose do not always result in proportional increases in serum levels. VPA dosage in monotherapy is correlated with both total and free plasma levels.[24] In situations involving the concomitant use of medications such as enzyme-inducing ASMs, VPA dosage should be increased to account for the influence of clearance.[8]

The strength of the current study lies in the use of chart reviews along with the therapeutic drug monitoring database in the hospital, which provides real-world data on patients with epilepsy. Additionally, we used inpatient data to ensure compliance with valproate therapy, thereby reducing issues related to noncompliance and increasing the accuracy of sampling times.

Several limitations should be acknowledged. First, we were only able to measure total (bound) VPA levels, without assessing the free (unbound) form of VPA. Due to high protein binding, total VPA levels may not accurately reflect the active free fraction of the drug in certain clinical scenarios, including uremic patients, individuals with chronic liver disease, and patients with hypoalbuminemia, Additionally, suspected drug–drug interactions, where one strongly protein-bound

Table 2

Factors affecting subtherapeutic VPA levels.

	Univariate analysis		Multivariate analysis	
Parameters	**OR (95%CI)**	***P***	**OR (95% CI)**	***P***
Demographics				
Male	2.20 (1.07–4.51)	.02	2.45 (1.15–5.22)	.02
Previous medication				
Phenytoin	2.87 (1.33–6.17)	.01	2.58 (1.16–5.71)	.02
VPA administration				
Syrup	3.43 (1.13–10.39)	.02	3.28 (1.12–9.68)	.03
VPA (mg/kg/day)				
<15	2.33 (1.05–5.19)	.04	2.34 (1.05–5.19)	.04
Co-medications				
Topiramate	6.01 (1.32–27.32)	.02	6.21 (1.27–30.74)	.02
Meropenem	4.34 (1.05–17.74)	.047	4.27 (1.04–17.46)	.04

VPA = valproic acid.

drug displaces another, such as phenytoin,[25] must also be considered, particularly in settings such as intensive care units.[26] Hypoalbuminemia is a key predictor of discordance between total and free VPA levels. Although there were no significant differences in serum albumin levels between groups, the lack of standardized guidelines for adjusting VPA dosing in patients with hypoalbuminemia[27] further complicates the interpretation of VPA levels in these cases. Regarding drug interactions, while we collected data on carbapenems, which have been shown in previous studies to significantly interact with VPA,[9,28] we only included meropenem in our analysis. This was due to the absence of patients in the therapeutic group receiving other carbapenems, which prevented appropriate statistical analysis. Additionally, in logistic regression analysis, ertapenem and imipenem were dropped from the model because it perfectly predicted subtherapeutic levels, further limiting our ability to assess its impact. Second, we did not collect some essential clinical parameters, such as seizure type and frequency, because this information is not routinely recorded in medical records. This could potentially skew our results as the relationship between VPA levels and seizure control may vary depending on these unrecorded variables. Third, we were unable to measure VPA levels in all epilepsy patients. Consequently, the proportion of patients with subtherapeutic VPA levels might have been underestimated or overestimated. These limitations highlight potential sources of bias and imprecision in our study. Missing clinical parameters and incomplete VPA data may affect the reliability and generalizability of our findings.

Our results suggest the importance of individualized dosage regimen to maintain effective VPA levels and to optimize patient outcomes. Further research should explore the underlying mechanisms of these associations to improve the therapeutic strategies for epilepsy management.

In conclusion, our study identified key factors associated with subtherapeutic VPA levels, including males, use of phenytoin, topiramate, and meropenem, as well as specific VPA administration routes and dosages. Clinicians should be aware of these factors when prescribing VPA to inpatients, enabling more effective monitoring and dosage adjustments to maintain therapeutic levels and optimize treatment outcomes.

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