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Factors Influencing Sodium Valproate Serum Concentrations in Patients with Epilepsy Based on Logistic Regression Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: We aimed to explore the risk factors that affect the serum concentration of sodium valproate (VPA-Na) in patients with epilepsy and to provide references for the rationale of the use of VPA-Na.

Material/Methods: The enzyme-multiplied immunoassay technique was used to determine the serum VPA-NA concentrations of 109 patients, and the results were retrospectively analyzed and summarized. A multivariate logistic regression model was used to analyze substandard serum VPA-Na concentrations.

Results: Fifty-six patients (51.38%) treated with VPA-Na tablets were within the effective treatment range of 50-100 μg/mL, while 53 patients (48.62%) were out of the treatment range. The results indicated that the standard-reaching rate of serum drug concentration in the juvenile group was higher than that in the adult and elderly groups; the standard-reaching rates of serum drug concentrations in the low-dose group and the intermediate-dose group were lower than that in the high-dose group; and the standard-reaching rate of serum drug concentration in the group receiving carbapenems in combination was lower than that in the non-combination group; all differences were statistically significant. The combination with carbapenems and enzyme inducers was an independent risk factor for VPA-Na serum concentration below the target level in hospitalized patients.

Conclusions: To improve clinical efficacy and reduce the occurrence of adverse reactions, there is a need for therapeutic drug monitoring of VPA-Na. Moreover, individual administration should be implemented when VPA-Na tablets are used in the treatment of epilepsy because of the significant fluctuation in VPA-Na blood concentration.

Keywords: Drug Monitoring • Epilepsy • Valproic Acid

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Background

Valproic acid (VPA), which is prepared as an injection, oral solution, sustained-release tablet, and ordinary tablet, is widely used to treat seizures, bipolar disorder, migraine, and other psychiatric illnesses or neuropathies [1]. Its mechanism of action involves the interruption of γ-aminobutyric acid (GABA) transferase decomposition, which causes an increase in the concentration of GABA in the brain and inhibits neuronal excitement by weakening the neuronal response to N-methyl-D-aspartic acid. Therapeutic drug monitoring of VPA is a key aspect of the drug treatment of epilepsy because the therapeutic window of VPA is relatively narrow and there are many factors that affect the serum drug concentration. The current reference treatment range of VPA for epilepsy recommended by existing guidelines is 50 to 100 mg/L [2,3]. When the serum drug concentration is lower than required for treatment, the symptoms of epilepsy are not well controlled, and when the concentration is exceeded, the risk of adverse drug reactions increases, including those of the digestive system, nervous system, and hematological system [4]. This study aimed to provide an individualized reference for rational clinical drug use based on the monitoring of clinical therapeutic drugs to explore the influence of various factors on the serum concentration of VPA. We collected relevant clinical data of patients treated with sodium valproate (VPA-Na) and analyzed them by logistic regression analysis.

Material and Methods

General Information

This study protocol was reviewed and approved by the Ethics Committee of the First People's Hospital of Nanning. Data were collected on 109 hospitalized patients who received oral VPA-Na medication and serum concentration monitoring in a class-A tertiary hospital in Guangxi from January 2018 to December 2019. Collected data included basic patient characteristics (sex, age), drug use information (dosage, dosage form, combination of drugs), and liver and kidney function, measured by alanine transaminase (ALT), aspartate transaminase (AST) albumin, creatinine, urea, uric acid, and cystatin C levels.

Inclusion Criteria

The patients met the diagnostic criteria for epilepsy in the "Guidelines for Clinical Diagnosis and Treatment - Epilepsy Volume" (2015 revised edition). After the patients had taken 5 to 6 doses of VPA-Na, blood samples were collected within the following 30 min.

Exclusion Criteria

Patients were excluded from the study for incomplete clinical medical records; poor compliance with the prescribed medications; steady-state concentration not reached; blood sampling monitoring after the patients took VPA-Na; serum concentration monitoring not performed; and pregnancy or lactation.

Instruments and Reagents

The following instruments and reagents were used: VPA detection kit (Siemens, USA) and Viva-E automatic biochemical analyzer (Siemens, USA).

Methods

After the VPA-Na serum concentration reached a steady state in patients treated with VPA-Na by the oral route, 5 mL of fasting venous blood was collected before the patients took the medication the next morning. Blood samples were centrifuged at 4000 rpm to collect the serum. The drug concentration of VPA-Na was determined by enzyme-multiplied immunoassay with the Viva-E analysis system. The treatment window of VPA-Na ranged from 50 to 100 mg/L. If the result was within the treatment window, it was classified as reaching standard requirements; otherwise, it was classified as failing to meet standard requirements.

Statistical Analysis

Data with a normal distribution were shown as mean±standard deviation, while non-normally distributed data were represented by median of the interquartile range (IQR, P25, P75), and the means of each group were compared. The independent samples were analyzed using the *t* test, and count data were expressed as a rate (%) and were analyzed using the chi-squared test. A *P* value of <0.05 was considered statistically significant. To screen and analyze the factors affecting the serum concentration of VPA-Na, we used logistic regression analysis. All statistical analyses were performed using SPSS version 16.0 (IBM Corp, Armonk, NY, USA).

Results

General Data

Therapeutic drug monitoring data were collected from 109 patients, including 83 male patients and 26 female patients. The patients' ages ranged from 3 months to 91 years, with an average age of 47.46±29.29 years. The daily dose of the patients was 0.2 to 1.8 g, so that the average serum concentration of VPA-Na was 52.47±26.26 μg/mL. The serum drug concentration

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Table 1. Demographic characteristic of patients.

Item	Standard concentration group (n=56)	Substandard concentration group (n=51)
Sex (F/M)	44/12	38/13
Age (years)		
0-13	18	5
14-60	17	24
≥60	21	22

Table 2. Chi-squared test of standard-reaching rate of VPA serum concentrations by single-factor analysis.

Variable		n (Standard concentration)	n (Substandard concentration)	(% of all)	*P*
Age/years	≤13	18	5	78.3%	0.015
	14-59	17	24	41.5%	
	≥60	21	22	48.8%	
Sex	Male	44	38	53.7%	0.620
	Female	12	13	48%	
Daily dose	≤0.5	18	10	64.3%	0.020
	0.5-1	26	37	41.3%	
	>1	12	4	75%	
Dosage form	Non-sustained release dosage form	45	44	50.6%	0.414
	Sustained-release dosage form	11	7	61.1%	
Hepatic function	Normal or mild injury	3	2	60%	1.000
	Severe injury	53	49	52%	
Renal function	Normal or mild injury	5	10	33.3%	0.1120
	Moderate to severe	51	41	55.4%	
Carbapenems	No	55	34	61.8%	0.0001
	Combination	1	17	5.6%	
Enzyme inducer drugs	No	52	33	61.18%	0.01
	Combination	4	18	18.18%	

of 56 patients (51.38%) was within the reference range; the serum drug concentration of 51 patients (46.79%) was below the lower limit of the reference value; and the remaining 2 patients had serum concentrations above the upper limit of the reference value (**Table 1**).

Clinical Data

First, we carried out univariate analysis. To facilitate the discussion and accurate conclusions, the data of the 2 patients exceeding the upper limit of the reference value were eliminated, and the chi-squared test was used to calculate the difference of the standard-reaching rate under the influence of a single factor. The chi-squared test results showed no significant differences in the standard-reaching rate of serum drug concentrations in groups divided by sex, dosage form, liver function, kidney function, and combined enzyme inducer. However, there were significant differences in the standard-reaching rate of serum drug concentration in other groups, such as the juvenile and high-dose groups. The standard-reaching rate in the juvenile group was higher than that in the mature group and elderly group; the rate was lower in the low-dose group and

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Table 3. Result of multi-logistic regression analysis for VPA serum concentration lower than the standard.

	β	SE	Wald	*P*
Carbapenems	3.62	1.08	11.34	0.001
Enzyme inducer drugs	1.36	0.55	6.11	0.013

intermediate-dose group than in the high-dose group; and in the group receiving carbapenems in combination, the standard-reaching rate was lower than that in the non-combination group (**Table 2**).

The second part of the study used multiple logistic regression to analyze VPA-Na serum concentrations lower than the standard. According to the results of the influence of a single factor and after excluding the data of the 2 patients whose concentrations exceeded the upper limit of the reference value, the variables mentioned above were analyzed by binary logistic regression. We showed that the combination of carbapenems and enzyme inducers was an independent risk factor for VPA-Na serum concentration below the target level ($P<0.05$). The results indicated a goodness of fit of 0.882 by the Hosmer-Lemeshow test (**Table 3**).

Discussion

This study analyzed the overall distribution of serum concentration of VPA-Na in hospitalized patients. The standard-reaching rate of the serum concentration of VPA-Na in our hospital was lower than that reported in other studies [5]. Owing to the more acute and severe hospitalized patients in our hospital, combined drug use was more common in the clinic, which led to substandard drug concentrations. Another reason may be that our physicians were more conservative in the selection of antiepileptic drugs for treatment, and the initial dose selected was the minimum dose. In addition, there was a high probability of patient noncompliance, which is why physicians generally did serum monitoring of VPA-Na only when combining drugs that may have significant interactions or when the patients did not respond well.

We evaluated the relationship between the serum concentration of VPA-Na and age and dosage. It has been reported that the dosage of VPA-Na and serum concentration is not a linear relationship, meaning that serum concentration did not increase proportionally with the increase in dose. When the drug dose is increased, the patient's blood drug concentration may not increase accordingly, which could be because the drug clearance rate has also increased [6]. This was somewhat different from our results, which showed that the compliance rate of the low-dose group was higher than that of the intermediate-dose group. The reason may be that the low-dose patients were mainly children and teenagers. In addition, due to the large number of basic diseases in elderly patients, multiple drugs were commonly used together, which may have affected the absorption and metabolism process of VPA-Na in vivo. Combined with the decline of physiological function in elderly patients, the drug combination was more likely to lead to a VPA-Na concentration below the target value.

In this study, we found that the liver drug enzyme reduced the half-life of VPA-Na in the body and accelerated its metabolism. When a patient was also treated with liver drug enzyme inducers, such as phenobarbital [7], phenytoin [8], and carbamazepine [9], we found that the liver drug enzymes reduced the half-life of VPA-Na in the body and accelerated its metabolism, thereby reducing the concentration of VPA-Na. The serum concentration of VPA-Na was affected mainly because the liver drug enzyme inducers reduced the half-life of the drug in vivo by enhancing the activity of cytochrome P450, which led to the accelerated metabolism of VPA-Na. Previous studies have indicated that the combination of drugs mentioned above not only reduces the serum concentration of VPA-Na, resulting in poor therapeutic effects, but also significantly increases the liver toxicity of VPA-Na [10,11]. For epilepsy, the treatment with VPA-Na alone was the recommended option. However, patients needed to use multiple drugs due to their medical conditions. To reduce adverse reactions, serum concentrations of VPA-Na should be monitored regularly, and the medication regimen should be comprehensively formulated according to the actual situation, while patients' liver and kidney function should be regularly evaluated.

Carbapenems, including imipenem, meropenem, ertapenem, panipenem, and biapenem, are the most widely used antibacterial drugs in critically ill patients. To date, most studies [12-14] have shown that carbapenems can significantly reduce the blood concentration of VPA-Na in the body. In the present study, of the 18 patients who also received meropenem or biapenem, only 1 reached the lower limit of the effective concentration, and the compliance rate was only 5.6%, which was far lower than the compliance rate of patients on non-combination therapy. Therefore, meropenem and other carbapenem drugs should not be used in combination with VPA-Na. For some critically ill patients who need to use carbapenem drugs and antiepileptic drugs concomitantly, it is recommended to give propylene and antiepileptic drugs rather than valeric acid [15,16].

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Limitations and Problems

There were some limitations in our study. First, the sample size was relatively small, with only 2 patients having serum drug concentration greater than the upper limit of the treatment window, which led us to study only the factors leading to substandard concentration in the multivariate regression analysis. Second, the therapeutic effects and toxicities of VPA-Na were affected by the target receptors, effector pathways, absorption, metabolism, and polymorphisms of transporter-related genes [17,18], but the polymorphisms of genes [19] were not included in this study. Studies [20,21] have shown that the genetic polymorphisms of CYP450ABCB1 and UGT genes are significantly related to the serum concentration of epilepsy patients treated with VPA-Na. Third, the effective therapeutic concentration of VPA-Na remains controversial; in this study, 50 to 100 μg/mL was considered the target value. However, some studies have shown that the type of disease onset should be considered in the selection of effective therapeutic concentrations because sometimes patients' conditions could be well controlled even with the concentration lower than 50 μg/mL, whereas some patients can need excessive drug concentration to control the disease, but with careful monitoring of liver function and routine blood parameters.

Conclusions

Considering the serum concentration in hospitalized patients is often lower than the standard concentration, clinical pharmacists may benefit from our study by adjusting the serum concentration of VPA-Na. For patients with a low dose or combined use of an enzyme inducer, a dose increase can be used to reach the standard drug concentration. Meanwhile, it is necessary to continuously monitor drug concentrations after the adjustment of the medication regimen to avoid great fluctuations. When possible, patients using non-sustained-release dosage forms should switch to sustained-release dosage forms. For patients who must be fed nasally, oral liquids or plain tablets are recommended, as grinding can destroy the special structure of the sustained-release tablets. The combined use of carbapenems should be avoided as much as possible. If the combined use of carbapenems is necessary, clinical pharmacists should select drugs other than VPA-Na, according to the type and frequency of seizure attacks.

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