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Research Article
*CYP3A5*3* Polymorphism May Influence the Concentration of Valproic Acid

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Abstract

Background and Objectives: *CYP3A5*3* with higher frequency was found to affect the metabolisms of many drugs such as tacrolimus and maraviroc and was proved to be one of the major factors influencing the inter-individual discrepancy in different races. In the present study, the effect of *CYP3A5*3* on the plasma concentration and efficacy of valproic acid (VPA) was analyzed to explore the role of *CYP3A5*3* in the inter-individual discrepancy. **Methodology:** A total of 64 children with epilepsy who administered by VPA were recruited. Then, serum VPA concentrations were measured by direct chemiluminescence assay and the polymorphism of *CYP3A5* (rs776746) was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Difference among the *CYP3A5* allele on dose, concentration, adjusted concentration (AC), concentration-dose ratio and efficacy of VPA was analyzed by one-way ANOVA or t test. **Results:** Doses for GG carriers were significantly higher than those for AG carriers ($p = 0.037$). Moreover, both AC and concentration-dose ratio in patients carrying GG genotype were lower than those in AG type patients ($p = 0.049$, $p = 0.001$). However, there was no statistical difference in the frequency of *CYP3A5*3* type among controlled, improved and uncontrolled-seizure groups ($p = 0.9$). **Conclusion:** The GG genotypes could decrease the AC and concentration-dose ratio of VPA which might provide a potential mechanism underlying inter-individual discrepancy of VPA, however, *CYP3A5*3* did not influence the efficacy of VPA.

Key words: *CYP3A5*3*, polymorphism, valproic acid, adjusted concentration, concentration-dose ratio, efficacy

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Valproic acid (VPA) was an old antiepileptic drug used for epilepsy for 50 years by virtue of its widely scope effects and kind tolerance[1]. It had been advised by the current National Institute for Health and Care Excellence guidelines as the first line therapy for epilepsy. Due to its wide variation of response, reference range from 50-100 μg mL^{-1} was recommended for the VPA monitoring[2]. Increasing studies had determined that age, environment and metabolism discrepancy contribute to the discrepancy of response to VPA.

The biotransformation of VPA consists of three major metabolic pathways, including uridine diphosphate glucuronosyltransferase (UGT) enzyme pathway, mitochondria β-oxidation way and cytochrome P450 (CYP) pathway, accounting for 50, 40 and 10%, respectively[3]. Many researchers had explored that polymorphism of major metabolic enzymes affected the concentration of VPA, however, it was still controversial.

For the UGT enzyme, Munisamy *et al.*[4] and Feng *et al.*[5] showed that the mutant type of UGT1A4 might lead to an extended half-life, decreased rate of clearance of VPA and caused high concentrations. However, Chatzistefanidis *et al.*[6] and Chu *et al.*[7] found no alternation of concentration between patients carrying mutant type of UGT1A4 (541A>G, 552A>C) and wild type. With respect to UGT2B7, studies displayed that the mutant type (C802T) of UGT2B7 could decrease the VPA concentration, however, no influence was found in other studies. Disputes also were found in the studies of UGT2B7 161C>T [8-10].

Besides, *CYP2A6*, *CYP2B6*, *CYP2C9* and *CYP2C19* were proved to be involved in the metabolic pathway from VPA to 4-ene-VPA[11]. It was showed that the polymorphism of *CYP2A6*4* and *CYP2B6*6* tended to increase the VPA concentration[12]. However, many researches showed that *CYP2C9*2*, *CYP2C9*3* and *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*4*, *CYP2C19*17* did not affect the VPA concentration[13,14]. Actually, *CYP2A6* and *CYP2B6* were not the major enzymes in liver or kidney. On the contrary, CYP3A4/3A5 in liver metabolized about 70% of drugs. It is found that the polymorphism of *CYP3A5*, not *CYP3A4*, contributed to the inter-individual variability of drugs[15]. *CYP3A5*3* variant, as a single nucleotide polymorphism in intron 3, was the best characterized genetic polymorphism in *CYP3A5*[16]. More studies have confirmed that *CYP3A5*3* are involved in many other diseases, including hypertension and acute leukemia[17,18]. It also plays an important role n the clearance of tacrolimus, sirolimus and lapatinib[19,20]. However, few studies were focused on the VPA plasma concentration. Hence, in this study, the effects of *CYP3A5*3* on the plasma concentration and efficacy of VPA were explored.

MATERIALS AND METHODS

Patients: Epilepsy children who were prescribed with VPA for more than three weeks were included in the retrospective study. Patients who had experienced no seizures for more than half a year, or with a decrease of more than 50% of seizures, or continued to experience seizures during VPA monotherapy or polytherapy were classified into controlled-, improved and uncontrolled-seizure group, respectively.

Determination of VPA concentration: Steady-state concentrations were determined by direct chemiluminescence assay by Viva-E equipment (Siemens), while the linear range was 26.8-150 μg mL^{-1}. In order to eliminate error from different weight and dosage, plasma concentration was standardized and expressed as adjusted concentration (AC) = plasma concentration/(daily dose/body weight) [μg kg/(mL g)], or concentration-dose ratio = plasma concentration/daily dose [μg/(mL g)].

Genotyping procedures: Residue of plasma was collected after the determination of VPA concentration. Genomic DNA was extracted from blood specimens by TIANamp DNA Blood Mini Kit (TIANGEN, Beijing, China) according to the manufacturer's instructions. The *CYP3A5*3* polymorphism was determined by a method based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) according to previously reported procedures[21]. Genomic DNA (50 ng) was amplified by TaKaRa Ex Taq (TaKaRa, Dalian, China) containing 0.05 mm Mg^{2+}, 25μM dNTP mixture, 1 μM each of forward primer (5′-CTT TAA AGA GCT CTT TTG TCT CTC-3′) and reverse primer (5′-CCA GGA AGC CAG ACT TTG AT-3′) and 1.25 units Ex Taq. Amplification was performed in an i-Cycler thermal cycler (Bio-Rad, Tokyo, Japan). PCR was conducted with an initial denaturation step at 95 for 10 min; amplified for 37 cycles at 94 for 30 sec, 56 for 30 sec, 72 for 30 sec and a final extension step at 72 for 7 min. After that, the PCR products were digested for a minimum 2 h at 37 with 5 units of Dde. Then the digested products were electrophoresed on 3% agarose gels. Genotypes were assigned according to fragment sizes (107, 71 and 22 bp product in heterozygote of *CYP3A5*3* allele, while 129 and 71 bp in the wild-type). The accuracy of the PCR-RFLP method was confirmed by direct sequencing of the amplified PCR product.

Statistical analysis: The deviation of genotyping data from the Hardy-Weinberg equilibrium was analyzed by χ^2 test. One-way ANOVA (Turkey test) and student's t-test were used to compare quantitative variables, including gender, age, body weight, dose, dosage per weight, concentrations and the distributions of patients taking VPA among AA+AG and GG genotypes[22]. All statistical analysis were performed by Prism 5.0 software. Difference was considered significantly when $p<0.05$.

RESULTS

Demographic characteristic: A total of 64 children were recruited and the demographic characteristics are shown in Table 1. The distribution of *CYP3A5*3* was consistent with the Hardy-Weinberg equilibrium ($\chi^2 = 0.32$, $p = 0.8$).

Effects of *CYP3A5*3* polymorphism on the concentration, AC and concentration-dose ratio of VPA: There was no statistical difference among AA, AG and GG carriers in age, body weight and plasma concentration. However, the doses prescribed for GG carriers were significantly higher than those AG carriers ($p = 0.037$). Moreover, both AC and concentration-dose ratio in patients who carrying GG genotype were lower than patients carrying AG genotype ($p = 0.049$, $p = 0.001$) (Table 2).

Effects of *CYP3A5*3* on the AC and concentration-dose ratio in monotherapy and polytherapy: In order to explore whether the effect of *CYP3A5*3* was related to the interaction of antiepileptic drugs, patients were divided into monotherapy and polytherapy groups. Results showed that the AC and concentration-dose ratio of GG carriers with monotherapy were slightly decreased, compared with AG carriers, however, there was no statistical discrepancy. Regarding to polytherapy, the mean concentration-dose ratio in children carrying GG was significantly lower than that in children with AG type ($p = 0.011$) (Table 3).

Relationship between the efficacy of VPA and plasma concentration, AC, concentration-dose ratio and *CYP3A5*3* polymorphism: Because of the lower AC and concentration-dose ratio in GG carriers, whether the frequency of GG or AG genotype was related to the efficacy of VPA was analyzed further. Results showed that there was no statistical difference neither in the frequency of *CYP3A5*3* genotype nor in the

Table 1: Demographic data, concentration and polymorphism of *CYP3A5*

Parameters	Values
Age (Years)	4.84±0.41
Gender (Male/female)	44 (68.7%)/20 (31.3%)
Body weight (kg)	20.03±1.300
VPA dose (g day^{-1})	0.48±0.035
Plasma VPA concentration (μg mL^{-1})	75.62±4.490
AC [μg kg/(mL g)]	3562.00±397.3
Concentration-dose ratio [μg/(mL kg)]	187.60±12.90
Antiepileptic therapy	
Monotherapy	
VPA	38 (59.4%)
Double medications	
+LEV	8 (12.5%)
+TPM	7 (10.9%)
+CZP	2 (3.1%)
+OXC	2 (3.1%)
+VGB	1 (1.6%)
Triple medications	
+LEV+TPM	3 (4.7%)
+LEV+CZP	1 (1.6%)
+CZP+LTG	1 (1.6%)
+CZP+TPM	1 (1.6%)
CYP3A5 polymorphism	
AA	5 (7.8%)
AG	29 (45.3%)
GG	30 (46.9%)

AC: Adjusted concentration, LEV: Levetiracetam, TPM: Topiramate, CZP: Clonazepam, OXC: Oxcarbazepine, LTG: Lamotrigine, VGB: Vigabatrin. The values were showed as Mean±SEM in age, body weight, VPA dose, plasma VPA concentration, AC and concentration-dose ratio. Values of gender and antiepileptic therapy were expressed with number of patients (%)

Table 2: Effects of *CYP3A5*3* polymorphism on dose, plasma concentration, AC and concentration-dose ratio of VPA

Polymorphism of *CYP3A5*	No. of patients	Age (Years)	Gender (M/F)	Body weight (kg)	VPA doses (g day^{-1})	Plasma VPA concentration (μg mL^{-1})	AC [μg kg/(mL g)]	Concentration -dose ratio [μg/(mL g)]
AA	5	4.7±1.7	3/2	17.80±3.7	0.50±0.14	87.62±23.37	3085±505.7	189.0±31.8
AG	29	4.4±0.67	22/7	19.40±2.3	0.40±0.039	82.18±7.0	4481±809.8	231.6±21.8
GG	30	5.3±2.9	19/11	20.95±1.6	0.56±0.059	67.27±5.6	2754±247.9	144.8±13.31
AA+AG	34	4.5±0.62	25/9	19.20±2.0	0.42±0.038	82.98±6.7	4275±697.5	225.3±19.20
AG+GG	59	4.85±0.43	41/18	20.21±1.38	0.48±0.037	74.60±4.51	3603±429.0	187.5±13.79
AA vs AG vs GG		0.825		0.76	0.4	0.371	0.394	0.09
AA vs AG		0.878		0.775	0.407	0.778	0.487	0.441
AA vs GG		0.707		0.468	0.699	0.220	0.61	0.217
AG vs GG		0.335		0.591	0.037*	0.098	0.049*	0.001**
AA+AG vs GG		0.314		0.508	0.049*	0.076	0.046*	0.001**
AA vs AG+GG		0.924		0.623	0.0138*	0.441	0.73	0.975

VPA: Valproic acid, values were showed as Mean±SEM in age, body weight, dose and concentration, *p<0.05 and **p<0.01

Table 3: Effects of *CYP3A5*3* on the AC and concentration-dose ratio of monotherapy and polytherapy

	No.(%)		AC [μg kg/(mL g)]		Concentration-dose ratio [μg/(mL kg)]	
Polymorphism of *CYP3A5*	Monotherapy	Polytherapy	Monotherapy	Polytherapy	Monotherapy	Polytherapy
AA	4 (6.2)	1 (1.6)	2812±550.4	4173	201.5±37.7	139.1
AG	18 (28.1)	11 (17.2)	3622.5±609.9	5885.1±1867.7	212.3±22.5	263.2±44.1
GG	16 (25)	14 (21.9)	2696.9±353.2	2818.7±358.7	162.5±21.8	124.7±12.7
AA vs. GG			0.881	-	0.41	-
AG vs. GG			0.213	0.136	0.124	0.011*

VPA: Valproic acid, values of AC and concentration-dose ratio were analyzed with Mean±SEM, *p<0.05

Table 4: Relationship between the efficacy and plasma concentration, AC, concentration-dose ratio and *CYP3A5*3* polymorphism

Plasma concentration and polymorphism of *CYP3A5*	Controlled-seizure group	Improved-group	Uncontrolled-seizure group	p-value
Plasma VPA concentration (μg mL^{-1})	76.49±9.2	72.75±7.1	78.37±7.4	0.849
AC [μg kg/(mL g)]	2827±342.2	3329±428.3	4096±852.8	0.883
Concentration-dose ratio [μg/(mL g)]	183.1±14.4	181.9±16.5	195.5±26.2	0.499
AA	3 (4.7%)	1 (1.6%)	1 (1.6%)	
AG	12 (18.7%)	4 (6.2%)	13 (20.3%)	
GG	13 (20.3%)	5 (7.8%)	12 (18.7%)	0.888

VPA: Valproic acid, values of plasma VPA concentration, AC and concentration-dose ratio were analyzed with Mean±SEM

plasma concentration, AC and concentration-dose ratio among the controlled-improved and uncontrolled-seizure groups. It suggested that *CYP3A5*3* might not affect the efficacy of VPA (Table 4).

DISCUSSION

In this study, it was showed that *CYP3A5*3* decreased the AC and concentration-dose ratio of VPA. *CYP3A5* was a major enzyme in CYP3 family and an important deliver of the metabolic clearance of tacrolimus and maraviroc in individuals[23-25]. While, *CYP3A5*3* (rs776746), which showed high frequency and could alter the structure of the enzyme and resulted in less capacity of CYP enzyme, was thought to be involved in the variability of drugs in different races[16]. Researches had demonstrated that *CYP3A5*3* carrier tended to have higher concentrations of quetiapine and simvastatin in blood[26,27]. However, we found that *CYP3A5*3* reduced the adjusted VPA concentrations, which was discordant with the mechanism that the mutant of *CYP3A5* should lead to less activity and thus a higher concentration. This might be ascribed to the expression and activity of *CYP3A5* in children who carrying *CYP3A5*3* and supposing to owe a lower concentration might also be instituted by other abundant enzyme such as *CYP3A4*. As is well known, *CYP3A4* and *CYP3A5* shared about 84% similarity in amino acid sequence. Kuang *et al.*[28] especially found that overexpression of *CYP3A5* could attenuate induction and activity of *CYP3A4* with inducer medication, suggesting that the expression of *CYP3A5* could interrupt the content of *CYP3A4* and the substantial activity of one isoenzyme might compensate for the reduced activity of another one[29]. In this research, it was interesting

that higher dosages were administered to GG carriers, on the contrary, their concentration in plasma were lower than AG carriers, which suggested that the children carrying GG allele might be less nonresponsive to VPA so that the higher doses were prescribed by the physicians.

The *CYP3A5* was proved to affect the response and resistance of many drugs, including the chemoresistance in pancreatic cancer patients, the resistance of imatinib mesylate and the efficacy of amlodipine[30-32]. However, in the present study, we found that there was no significant difference in the frequency of mutant *CYP3A5* among controlled-, improved- and uncontrolled-group, which implied that the mutation of *CYP3A5* was not directly related to the inefficacy or resistance of VPA, which agreed to some previous studies[33-34]. Meanwhile, the efficiency of VPA depended on various factors such as age, progression of epilepsy, age at onset therapy and plasma concentration, which were complicated[35].

CONCLUSION

The GG genotypes could decrease the AC and concentration-dose ratio of VPA which might provide a potential mechanism underlying inter-individual discrepancy of VPA, however, *CYP3A5*3* did not influence the efficacy of VPA.

SIGNIFICANCE STATEMENTS

The present study was planned to explore whether the role of *CYP3A5*3* in the inter-individual discrepancy *CYP3A5*3* decreased the AC and concentration-dose ratio of VPA which might account for the widely individual discrepancy of VPA *CYP3A5*3* could not affect the efficacy of VPA in Chinese epilepsy children.

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