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Effect of CYP2C19 polymorphisms on serum valproic level acid in Chinese Han patients with schizophrenia

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Valproic acid is an anticonvulsant, which is also widely used for treating psychiatric disorders. Some clinical trials have demonstrated benefits of valproic acid augmentation therapy in schizophrenia. Interindividual variability in valproic acid dose and serum concentration may reflect functional consequences of genetic polymorphisms in genes encoding drug-metabolizing enzymes. The aim of this study was to determine the relationship between serum concentrations of valproic acid and single nucleotide polymorphisms of the *cytochrome P450 (CYP) 2C19* gene in patients with schizophrenia. All patients had been receiving fixed dose of valproic acid for at least 2 weeks. The daily doses were 0.5–1.5 g. No other drugs except olanzapine were coadministered. Serum concentrations of valproic acid were measured using the ultra-high performance liquid chromatography method with mass-spectrometric detection. The *CYP2C19 (CYP2C19*2 G681A* rs4244285 and *CYP2C19*3 G636A* rs4986893) genotypes were identified by real-time PCR analyses. The mean concentration/dose ratios of valproic acid were significantly higher in patients with *CYP2C19 *1/*2* genotype (P < 0.01) or *CYP2C19 *2/*3* genotype (P < 0.01) than in those with *CYP2C12 *1/*1* genotype. The mean concentration/dose ratios of valproic acid were significantly higher in patients with 1 (P < 0.01) or 2 (P < 0.01) mutated alleles for *CYP2C19* than in those without mutated alleles. And the post hoc analysis revealed that the result has acceptable statistical (power (1 − β) = 0.8486 at type I level of 0.05) to support the observed significant associations for *CYP2C19* SNPs and serum C/D ratios of valproic acid. The findings of this study suggest that the genetic polymorphisms of CYP2C19 significantly affect the steady-state serum concentrations of valproic acid in Chinese Han population. The determination of the CYP2C19 genotypes may be useful for dosing adjustment in schizophrenia patients on valproic acid therapy.

Over the last 40 years, a variety of adjunctive treatments have been used to treat schizophrenia[1]. These are often used in addition to antipsychotics, in an attempt to alleviate the symptoms of schizophrenia such as hallucinations and delusional beliefs, although they have been used instead of antipsychotics. Valproate/valproic acid has been used for people whose psychosis did not respond to traditional therapy. Valproic acid is traditionally used as an anticonvulsant drug and is also used for affective disorders, especially for the treatment of acute mania[2]. Furthermore, it is thought to have anti-aggressive effects and it may reduce impulsive behaviour, which might be useful for some people with schizophrenia[3–5]. The dose of valproic acid and the plasma concentration may be significantly different among individuals due to genetic polymorphisms of cytochrome P450 (CYP) 2C19 and 2C9, or interactions with other drugs[6,7]. Optimizing the valproic acid dose with genetic variation could play a key role in individualized care to avoid adverse drug reactions or treatment failure and maximize drug efficacy[8].

The metabolism of valproic acid is complex. The major metabolic pathways of valproic acid comprise glucuronidation and mitochondrial β-oxidation, while CYP-mediated oxidation is only a minor pathway[9]. CYP2C19 plays a key role in the biotransformation of valproic acid in humans. There are significant racial differences in valproic acid transformation due to gene polymorphism[10].

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There is large interindividual variability in its pharmacokinetics and pharmacodynamics[7,11]. Therefore, its serum concentration needs to be monitored as a guide of dose adjustment during the course of therapy. Genetic factors have been reported to represent key factors that influence the pharmacokinetics variability of VPA. In particular, certain polymorphisms of cytochrome P450 2C19 (CYP2C19) has been shown to affect VPA pharmacokinetics[12,13]. Several mutated alleles of the *CYP2C19* locus that cause decreased enzyme activity, that is, *CYP2C19*2* (G681A rs4244285, splicing defect) and *CYP2C19*3* (G636A rs4986893, W212X, premature stop codon) have been reported[14,15]. The steady-state serum concentration of valproic acid is significantly dependent on the mutated alleles. However, there are large overlaps in these steady-state serum concentrations among the different genotype groups and considerable interindividual variations in the values within each genotype. In previous published studies, body weight, age, gender and comedications had significant influence on VPA distribution volume[16–18]. Although various genetic polymorphisms were associated with the increase or decrease of VPA serum concentration[6,12,19–24], only two study identified the quantitative relationship between genetic polymorphisms *CYP2C19* and VPA distribution volume in epileptic patients[6,25].

Therefore, we aimed to investigate the effects of various factors including CYP2C19 polymorphisms, age, gender, body mass index (BMI) and duration of schizophrenia on the steady-state serum concentrations of valproic acid in Chinese Han patients with schizophrenia, which might be useful for VPA dose adjustment in clinical practice.

Materials and methods

Participants. The subjects were 296 Chinese Han inpatients with schizophrenia (78 males and 218 females) who all fulfilled the criteria for schizophrenia. The inclusion criteria were as follows: (1) aged 18–60 years; (2) meeting the criteria of the International Classification of Diseases-Tenth Edition (ICD-10) for schizophrenia; (3) Han Chinese in origin; (4) normal liver and renal function; and (5) no substance abuse. The exclusion criteria included the following: (1) treatment-resistant schizophrenia; (2) pregnant or lactating women; and (3) with severe physical disease or brain organic disease, neurological disorder, delirium, or dementia. The mean ± SD of age and BMI value were 35.30 ± 12.40 years and 22.37 ± 4.14, respectively. 10 were smokers (≥ 10 cigarettes/day), whereas the remainders were nonsmokers. None was a heavy drinker. This study was approved by the Ethics Committee of the Hangzhou Seventh people's hospital (2,016,018), and all the patients had given written informed consent to participate in this study. All methods were performed in accordance with the relevant guidelines and regulations.

Drug treatment. All the subjects had received valproic acid for at least 2 weeks. It has been shown that plasma concentrations of valproic acid reach steady state by 2 weeks after repeated oral administration. The daily dose was fixed and was given twice a day. The patients were receiving no drugs except olanzapine (2.5–20 mg/day). Female patients did not receive oral contraceptives. Patients' adherence was confirmed by the nursing staff or their families. Blood samples were taken at 8 a.m.

Analytical methods. Serum concentrations of valproic acid were measured using the ultra-high performance liquid chromatography method with mass-spectrometric detection[26] by Zhejiang BIOZON Medical Co., Ltd. The lowest limit of detection for valproic acid was 2.5 µg/ml using 0.4 ml of serum, and the interassay coefficient of variation was 7.98% at a concentration of 50 µg/ml. The steady-state serum concentrations were adjusted by the doses of valproic acid, and the concentration/dose (C/D) ratios were used in statistical analyses.

DNA was isolated from peripheral leucocytes using a nucleic acid extraction and purification kit (Kuangyuan, Suzhou, China). The *2 and *3 alleles of *CYP2C19* were identified by PCR analyses using Human *CYP2C19* genotyping kit (Kuangyuan, Suzhou, China).

Statistical analyses. Demographic characteristics were compared by using Student's *t* test for continuous variables and χ^2 test for categorical variables. The serum C/D ratios of valproic acid of patients were compared among different genotypic groups or different metabolic type groups using one way ANOVA analyses with Bonferroni post hoc tests. Multiple linear regression analyses were used to detect the association between serum C/D ratios of valproic acid and several factors, including the polymorphisms of CYP2C19, age, gender, BMI value, smoke and duration of schizophrenia. A *P* value of less than 0.05 was regarded as statistically significant. SPSS Statistics 23.0 for Windows was used for these statistical analyses. Post-hoc power analyses were calculated using G*Power software (version 3.1).

Ethics approval and statement of consent to participate. The study was approved by the Ethics Committee of the Hangzhou Seventh People's Hospital. The purpose and importance of the study were explained to each participant before they proceeded into actual activities. Informed consent was obtained from their guardians or relatives.

Results

Influence of *CYP2C19* genotype on serum C/D ratios of valproic acid. To explore the effects of *CYP2C19* genotype on interindividual variabilities in serum concentrations of valproic acid in Chinese Han schizophrenia, the *CYP2C19*2* (G681A, splicing defect) and *CYP2C19*3* (G636A, W212X, premature stop codon) were analyzed by real-time PCR. The characteristics of study population and the frequencies of *CYP2C19* genotype are shown in Table 1. There were no significant differences in the general characteristics among genotypes.

	*1/*1	*2/*2	*3/*3	*1/*2	*1/*3	*2/*3	F/χ^2	p
Male/female, n	31/87	9/21	0/0	28/90	7/12	3/8	1.707	0.790
Age, years	35.25 ± 11.87	33.17 ± 11.19	–	34.17 ± 13.51	32.79 ± 12.15	31.27 ± 9.49	0.472	0.756
BMI	22.62 ± 3.62	22.55 ± 3.52	–	22.30 ± 4.69	20.37 ± 3.10	23.43 ± 5.73	1.420	0.227
Duration of schizophrenia, month	124.31 ± 102.39	90.27 ± 74.80	–	110.64 ± 119.52	101.47 ± 90.33	125.27 ± 122.35	0.762	0.551

Table 1. Characteristics of study population. *1/*1: 681GG, 636GG; *1/*2: 681GA, 636GG; *1/*3: 681GG, 636GA; *2/*2: 681AA, 636GG; *2/*3: 681GA, 636GA; *3/*3: 681GG, 636AA.

		VPA C/D ratio (µg/ml/g)			
Genotype	N	mean	SD	SE	95% CI
681GG, 636GG	118	90.96	46.46	4.28	82.49–99.43
681AA, 636GG	30	130.76 a	54.35	9.92	110.46–151.05
681GG, 636AA	0	–	–	–	
681GA, 636GG	118	131.37 a	50.33	4.63	122.19–140.54
681GG, 636GA	19	132.42 a	32.42	7.44	116.80–148.05
681GA, 636GA	11	172.25 a	83.54	25.19	116.13–228.38

Table 2. Steady-state serum C/D ratio of VPA between CYP2C19 genotypes. [a] $p < 0.05$ compared with group (681GG, 636GG).

		VPA C/D ratio (µg/ml/g)			
metabolic types	N	mean	SD	SE	95% CI
Homozygous EMs (*1/*1)	118	90.96	46.46	4.28	82.49–99.43
heterozygous EMs (*1/*2、*1/*3)	137	131.51 a	48.15	4.11	123.38–139.65
PMs (*2/*2、*2/*3、*3/*3)	41	141.89 a	65.06	10.16	121.35–162.43

Table 3. Steady-state serum C/D Ratio of VPA between CYP2C19 metabolic types. [a] $p < 0.01$ compared with Homozygous Ems; power $(1 − \beta) = 0.8486$ at type I level of 0.05. EMs: extensive metabolizers; PMs: poor metabolizers; *1/*1: 681GG, 636GG; *1/*2: 681GA, 636GG; *1/*3: 681GG, 636GA; *2/*2: 681AA, 636GG; *2/*3: 681GA, 636GA; *3/*3: 681GG, 636AA.

Furthermore, associations between *CYP2C19* SNPs and serum C/D ratios of valproic acid were observed. The number of patients with *CYP2C19* *1/*1, *1/*2, *1/*3, *2/*3, *2/*2 and *3/*3 genotype were 118, 118, 19, 11, 30 and 0, respectively (Table 2). Patients with *CYP2C19* *1/*2 ($P = 0.029$) or *CYP2C19* *2/*3 ($P < 0.01$) had significantly higher serum C/D ratios of valproic acid than those with *CYP2C19* *1/*1 (Table 2). And, the mean concentration/dose ratios of valproic acid were significantly higher in patients with 1 (heterozygous extensive metabolizers, $P < 0.01$) or 2 (poor metabolizers, $P < 0.01$) mutated alleles for *CYP2C19* than in those without mutated alleles (Table 3 and Fig. 1). And the post hoc analysis revealed that the result has acceptable statistical (power $(1 − \beta) = 0.8486$ at type I level of 0.05) to support the observed significant associations for *CYP2C19* SNPs and serum C/D ratios of valproic acid.

Multiple regression analysis. Multiple regression analysis including *CYP2C19* polymorphisms, age, gender, BMI values, smoke and duration of schizophrenia revealed that the polymorphisms of *CYP2C19* (standardized beta = 12.480, $P < 0.01$) and the BMI values (standardized beta = − 1.518, $P < 0.05$) were correlated with C/D ratios of valproic acid (Table 4).

Discussion

A number of reports have been published regarding the pharmacokinetics variability of antipsychotic. These data indicate substantial effects of select genotypes on the pharmacokinetics phenotype. As an important adjuvant drug in the treatment of schizophrenia, the blood concentration of VPA is also affected by genetic factors.

Although a number of reports have been published on the pharmacokinetic of valproic acid, mostly in epileptic patients, no study in schizophrenia patients. Therefore, we investigate the effects of CYP2C19 polymorphisms on the steady-state serum concentrations of valproic acid in Chinese Han patients with schizophrenia, which might be useful for VPA dose adjustment in clinical practice.

In this study, the mean serum C/D ratios of valproic acid increased in accordance with the number of the mutated alleles for *CYP2C19* in schizophrenia patients. It is the data that strongly implied that the mean serum C/D ratios of valproic acid increases in a gene dose-dependent manner. The mean concentration/dose ratios of
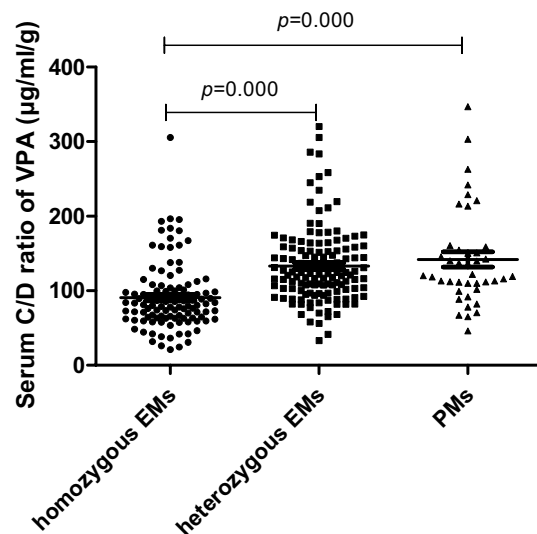
Figure 1. Differences in serum concentration/dose ratio of valproic acid in various metabolizer of CYP2C19 in Chinese schizophrenia patients. EMs: extensive metabolizers; PMs: poor metabolizers.

Variables	B	SE	Beta	t	p
(Constant)	99.380	21.735		4.572	0.000
CYP2C19 genotype	12.480	1.810	0.372	6.896	0.000
Gender	2.943	5.540	0.029	0.531	0.596
Age	0.606	0.332	0.138	1.826	0.069
BMI	− 1.518	0.706	− 0.116	− 2.151	0.032
Smoke	− 0.456	7.360	− 0.003	− 0.062	0.951
Duration of Schizophrenia	− 0.076	0.038	− 0.149	− 1.972	0.050

Table 4. Standardized partial correlation coefficients (Beta) between serum C/D ratio of VPA and various factors ($n = 298$, $R^2 = 0.170$). EMs: extensive metabolizers; PMs: poor metabolizers.

valproic acid were significantly higher in patients with 1 or 2 mutated alleles for *CYP2C19* than in those without mutated alleles. Importantly, the post hoc analysis revealed that the result has acceptable statistical (power $(1 − β) = 0.8486$ at type I level of 0.05) to support the observed significant associations for *CYP2C19* SNPs and serum C/D ratios of valproic acid. The result was assistant with previous report in epileptic[3], and it indicates that the influence of CYP2C19 polymorphism on serum concentration of VPA in schizophrenia is consistent with that of epilepsy patients. However, we just investigated the serum concentration of VPA in a very small part of schizophrenia patients treated with olanzapine and VPA. As for, that the effect of CYP2C19 polymorphism on serum concentration of VPA in schizophrenia patients treated with other antipsychotic drugs combined with VPA remains to be further observed.

In addition, multiple regression analyses showed that the serum C/D ratios of valproic acid were not only correlated with the number of mutated alleles for *CYP2C19* but also associated with the BMI values. One study showed that loss-of-function *CYP2C19* polymorphisms were associated with an increased BMI value[27]. This may explain the association between BMI values and the serum C/D ratios of valproic acid in our study. And some studies reported the effect of age on the metabolism of valproic acid[28,29], showed that there was no statistically significant difference in the rate of VPA metabolism. Another study showed that serum valproic acid levels was significantly increased with younger age[30]. These results are inconsistent. A larger population sample size is needed to further verify the results.

This study has several limitations. Glucuronidation and mitochondrial beta-oxidation (approximately 70–90%) are the major VPA metabolic pathway in adults[31]. We did not investigate the contribution of uridine diphosphate glucuronosyltransferase polymorphisms which are the most confounding factors to interindividual variations in valproate pharmacokinetics[32,33]. We also did not investigate the contribution of CYP2C9 polymorphisms which are the important factors to valproate metabolism[10,12]. Second, the sample is too small to derive greater statistical power because of the limited number of patients eligible for the trial, but our research may provide guidance on VPA dosing in schizophrenia patients. Third, the dose of valproic acid was not unified. Data of clinical responses related with the observed differences in the steady-state serum concentrations of valproic acid were lacking.

Conclusions

The findings of this study suggest that the genetic polymorphisms of CYP2C19 significantly affect the steady-state serum concentrations of valproic acid in Chinese Han population. The determination of the CYP2C19 genotypes may be useful for dosing adjustment in schizophrenia patients on valproic acid therapy.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Author contributions

S.W., M.S., J.S. were responsible for study design, X.J., J.L., C.W., J.S. were responsible for recruiting the subjects, S.W., J.L., P.Y., X.Y. were responsible for collecting clinical data and performing the clinical rating. S.W., J.L., P.Y. were responsible for statistical analysis, and manuscript. All authors contributed to and have approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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