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PHARMACOGENETICS

Influence of UDP-glucuronosyltransferase polymorphisms on valproic acid pharmacokinetics in Chinese epilepsy patients

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Abstract
Purpose The aim of this study was to investigate the genetic polymorphisms of UGT1A3, UGT1A6, and UGT2B7 in Chinese epilepsy patients and their potential influence on the pharmacokinetics of valproic acid (VPA).
Methods The genetic architectures of UGT1A3, UGT1A6, and UGT2B7 in 242 epilepsy patients were detected by DNA sequencing and PCR-restriction fragment length polymorphism. Steady-state plasma concentrations of VPA in 225 patients who had received VPA (approx. 250–1,000 mg/day) for at least 2 weeks were determined and associated with UGT polymorphisms.
Results The allelic distribution of UGT1A3 in our Chinese epilepsy patients was significantly different from that in healthy subjects based on reference data. The standardized trough plasma concentration (C_S) of VPA was much lower in our patients with the UGT1A3*5 variant than in the wild type carriers (3.24±1.05 vs. 4.68±1.24 μg·kg·mL^{-1}·mg^{-1}, $P<0.01$). UGT polymorphisms had no influence on the pharmacokinetic interactions between carbamazepine and VPA.
Conclusion Our results suggest that UGT1A3*5 may be an important determinant of individual variability in the pharmacokinetics of VPA and that it may be necessary to increase VPA dose for UGT1A3*5 carriers to ensure its therapeutic range of 50–100 μg/mL.

Keywords Valproic acid · UDP-glucuronosyltransferase · Polymorphisms · Pharmacokinetics · Drug combination

Introduction

Valproic acid (2-propylpentanoic acid, VPA) is an antiepileptic drug (AED) that has been in long use as an anticonvulsant medication in epilepsy and also used in the treatment of other brain diseases [1]. Recent studies have revealed that VPA is also a potential anticancer agent because of its inhibitory activity on histone deacetylase [2]. VPA has a narrow therapeutic range (50–100 μg/mL) in the treatment of epilepsy and shows considerable individual variability in both its pharmacokinetics and pharmacodynamics. Although the exact mechanisms of VPA individual variability remain elusive, drug co-medications and gene polymorphisms have been found to be two major causes [3–7].

VPA is extensively metabolized and dozens of metabolites are produced from oxidation catalyzed by various cytochrome P450s, mitochondrion-mediated β-oxidation, and glucuronidation catalyzed by uridine diphosphate glucuronosyltransferases (UGTs) [8, 9]. Glucuronide metabolites account for an up to 50% of the VPA dose [10, 11],

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suggesting a pivotal role of UGTs in VPA metabolism. UGT2B7, UGT1A3, and UGT1A6 are the major UGT isozymes involved in the production of VPA glucuronides [14, 15]. UGT isozymes were found to be highly polymorphic, and some of the polymorphisms can lead to both transcriptional and functional changes of the enzymes [12, 13]. The isozyme UGT2B7 shows the highest activity for VPA glucuronidation; however, its variant (UGT2B7*2, H286Y) has been found to have little influence on the pharmacokinetics of VPA in healthy volunteers [6]. UGT1A6*2 (T181A/R184S) possesses a twofold higher activity for catalyzing VPA glucuronidation in vitro than the wild type [16]. A total of 17 single nucleotide polymorphisms in UGT1A3 have been identified, and some of these showed functional significance [17–19]. However, currently available information on the influence of UGT polymorphisms on VPA pharmacokinetics is extremely limited, and no studies have been performed with epilepsy patients.

Given the pivotal role of UGTs in VPA metabolism, we hypothesized that genetic polymorphisms of the major UGT isozymes responsible for its metabolism, including UGT1A3, UGT1A6, and UGT2B7, are possibly important determinants of its pharmacokinetic inter-individual variability. We have therefore investigated the genetic polymorphisms of UGT1A3, UGT1A6, and UGT2B7 in a population of Chinese epilepsy patients, as well as their association with VPA pharmacokinetics. We also determined the potential influence of genetic polymorphisms on the pharmacokinetic interactions of co-administered carbamazepine with VPA.

Methods

Patients and blood sampling

A total of 242 epilepsy outpatients were enrolled between March 2008 and October 2009 at the department of Neurology at Jinling Hospital (Nanjing, China). All patients had been diagnosed with epilepsy, with normal liver and kidney function, based on their seizure history and the results of the electroencephalogram and biochemical laboratory tests. The protocol of this study was approved by the Ethics Committee of Nanjing Jinling Hospital, and written consent was obtained from all patients prior to enrollment.

Patients received sodium valproate (Deparkin; Sanofi-Synthelabo Minsheng Pharmaceutical, Hangzhou, China) (250–1,000 mg/day) or other AEDs to control epilepsy. The dosing regimen was maintained stably for at least 2 weeks (>5 half-lives) to ensure that the blood sampling was performed at the steady-state of VPA pharmacokinetics. Venous blood samples (5 mL) for analysis were collected immediately before the morning dose. The blood samples were separated into two tubes, one of which was centrifuged immediately to obtain plasma and then stored at −70°C until used for drug analysis, and the other was immediately stored at −20°C until used for DNA isolation.

Quantification of VPA plasma concentrations

Steady-state trough plasma concentrations of VPA were determined by a fluorescence polarization immunoassay (FPIA) performed using TDx equipment (Abbott Laboratories, Abbott Park, IL); this is a standard method applied in routine therapeutic drug monitoring (TDM) [20]. The method developed in this study was validated for biosample analysis in a linear range of 0.7–150 μg/mL; inter- and intra-batch variations were <10% and the lower limit of quantification (LOQ) was 0.7 μg/mL.

Genetic analysis of UGTs

Genomic DNA was extracted from peripheral blood lymphocytes using the blood DNA extraction kit according to the manufacturer's recommendations (BioMed, China). DNA concentrations were determined by spectrophotometry at 260 nm, and all samples were stored at −20°C until analysis. The presence of UGT1A6 (A541Gand A552C) and UGT2B7 C802T variants was identified by PCR-restriction fragment length polymorphism (RFLP) [21, 22]. UGT1A3 was genotyped directly by gene sequencing according to the manufacturer's instructions on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA), and analyzed with Gene Scan software (Applied Biosystems). Sequencing data were checked for the presence of six frequently identified single nucleotide polymorphisms (SNPs) including A17G, T31C, A81G, C133T, T140C, and A477G. The primers of UGT1A3 were designed using Primer Premier 5.0 software (Premier Biosoft, Palo Alto, CA). All primers were synthesized by integrated DNA technologies (Invitrogen, Shanghai, China); primers sequences, and specific annealing temperatures are listed in Electronic Supplementary Material (ESM) Table 1. Restriction enzymes (Fermentas, Ontario, Canada) for UGT1A6 and UGT2B7 are listed in ESM Table 2. In total, 5 % of the samples were randomly selected for validation by gene sequencing.

Statistical and computational genetic analysis

Hardy–Weinberg equilibrium analysis of UGT1A3, UGT1A6, and UGT2B7 SNPs was performed using Haploview 4.2 software (available at: www.broad.mit.edu/mpg/haploview). Allelic and genotypic frequencies of UGTs in our population of Chinese epilepsy patients were compared with those previously reported in Chinese healthy

volunteers and Japanese and German–Caucasian populations by the Fisher's Exact chi-square test.

Trough plasma concentrations of VPA were standardized by adjusting with patients' weight and dose and expressed as C_S [C_S=trough plasma concentration/(dairy dose/weight)] [23]. Data were expressed as mean± standard deviation (SD). Statistical differences in VPA C_S among various groups classified by genotypes and/or drug combinations were analyzed preferentially by nonparametric methods (Kruskal–Wallis and Mann–Whitney test for multiple comparisons); if the analysis was significant ($P<0.05$), a one-way analysis of variance (ANOVA) test with Dunnett's post hoc test was then applied to compare the difference between groups. A p value of <0.05 was considered to be significant. Statistical analysis was performed using SPSS ver. 16.0 software (SPSS, Chicago, IL).

Results

Clinical characteristics of epileptic patients

Genotyping was performed in a total of 242 epilepsy patients; 136 of these were treated with VPA monotherapy, while 38 were concomitantly treated with carbamazepine, 19 with topiramate, three with phenytoin, six with piracetam, and 23 with vitamins and cardiovascular agents. The remaining 17 patients received no VPA but other ADEs. All participants are from the Chinese Han population. Of these patients, 163 were male with an average [± standard deviation (SD)] age of 31.1 (±16.1) years, and 79 female, with an average age of 27.5 (±14.0) years. The average body weight was 64.7 (±17.0) and 55.0 (±12.4) kg for male and female patients, respectively.

SNPs, alleles, and haplotype analysis of UGT1A3, UGT1A6, and UGT2B7 in Chinese epilepsy patients

DNA samples from the whole blood of 242 patients were screened by RFLP-PCR and gene sequencing to determine the prevelance of UGT1A3, UGT1A6, and UGT2B7 polymorphisms in the Chinese epilepsy patients (Table 1). The allelic distributions of all SNPs detected in this study were consistent with Hardy–Weinberg equilibrium. As our study was the first to determine the distribution of UGT polymorphisms in epilepsy patients, we compared our findings with those previously identified in Chinese, Japanese, and Caucasian healthy volunteers [18, 24–30]. Previous studies found that UGT1A3 SNPs comprise four UGT1A3 allele variants, including UGT1A3*2b (T31C-G81A-T140C-A477G), UGT1A3*3b (T31C-G81A-A447G), UGT1A3*4 (C133T), and UGT1A3*5 (A17G-T31C-G81A-A477G) [18, 22, 31]. We identified significant differences between our Chinese epilepsy patients and healthy subjects for the gene frequencies of some of UGT1A3 alleles, including UGT1A3*1 (42 vs. 68 %, $P<0.05$), UGT1A3*2b (21 vs. 9 %, $P<0.05$), and UGT1A3*3b (18 vs. 7 %, $P<0.05$) (Table 2). In contrast, there was little difference in the genotype frequencies of UGT1A6 and UGT2B7 in our Chinese epilepsy patients and the healthy subjects (Table 3).

Haplotype analysis was performed among the eight SNPs of the UGT1 locus (UGT1A3 and 1A6) to determine their potential cooperative contributions in alternating the enzyme activity. A total of 20 haplotypes were identified (ESM Table 3). Dominant haplotypes include II (9.5%, UGT1A3*1–UGT 1A6 541 A>G-552 A>C), III (9.5%, all reference alleles except UGT1A3*3b), IV (8.68%, all reference alleles except UGT1A3*2b), V (6.20%, all reference alleles except UGT1A6 552 A>C), VI (5.79%, UGT1A3*2b–UGT1A6 541 A>G-552 A>C), and VII (5.79%, all reference alleles except UGT1A3*5); the frequencies of other haplotypes were less than 5% (ESM Table 3).

Association of UGT polymorphisms with VPA plasma trough concentrations

To determine the influence of polymorphisms of the identified UGTs on VPA pharmacokinetics, we conducted an association analysis of UGT SNPs, genotypes, and haplotypes with VPA C_S. Among all of the UGT SNPs detected, only the UGT1A3 A17G polymorphism showed a significant influence, with carriers of UGT1A3 A17G polymorphism characterized by having a much lower VPA C_S than the wild-type carriers (ESM Table 4). Patients who were carriers of UGT1A3*5 alleles harboring the A17G mutation were consistently characterized with a significant lower VPA C_S (Table 4), whereas polymorphisms of UGT1A6 and UGT2B7 had no significant effect on VPA C_S (Table 5). The same result was obtained from the association analysis of UGT1A haplotypes and VPA C_S, with only those patients with haplotype VII and XV, both harboring the UGT1A3*5 mutation, characterized with a significant lower VPA C_S (ESM Table 5).

Association of UGT polymorphisms with drug interactions

The patients receiving concomitant therapy with carbamazepine and VPA were characterized with a much lower VPA C_S than those receiving VPA monotherapy (3.53±1.67 vs. 4.57±1.48, $P<0.01$) (ESM Table 6). To determine whether UGT genotypes influence VPA–carbamazepine interactions, we sub-classified the patients receiving concomitent carbamazepine and VPA according to UGT genotypes and found no significant difference among the different patients (Table 6).

Table 1 Distribution of single nucleotide polymorphisms of uridine diphosphate glucuronosyltransferases in Chinese epilepsy patients (n=242)

Nucleic acid change	Amino acid changes	Frequency of SNP, n (%)			Hardy–Weinberg equilibrium P value
		Wild type	Heterozygote	Homozygote	
UGT1A3					
17 A>G	Q6R	215 (88.84)	27 (11.16)	0	0.658
31 T>C	W11R	114 (47.11)	110 (45.45)	18 (7.44)	0.465
81 G>A	E27E	113 (46.69)	112 (46.28)	17 (7.02)	0.309
133 C>T	R45W	221 (91.32)	21 (8.68)	0	0.780
140 T>C	V47A	183 (75.62)	55 (22.73)	4 (1.65)	0.998
477 A>G	A159A	116 (47.93)	110 (45.45)	16 (6.61)	0.326
UGT1A6					
541 A>G	T181A	157 (64.88)	79 (32.64)	6 (2.48)	0.561
552 A>C	R184S	139 (57.44)	97 (40.08)	6 (3.72)	0.359
UGT2B7					
802 C>T	H268Y	109 (45.04)	114 (47.11)	19 (7.85)	0.348

UGT, Uridine diphosphate glucuronosyltransferase; SNP, single nucleotide polymorphism

Discussion

Uridine diphosphate glucuronosyltransferases have been previously proven to be highly polymorphic, and their genetic polymorphisms have been associated with altered metabolism of many endogenous and exogenous compounds and with the susceptibility to various diseases [32–35]. Although there have been several previous reports of an association between UGT polymorphisms and VPA pharmacokinetics, none of these studies involved epilepsy patients. In one study, genetic polymorphisms of UGT2B7, the UGT isozyme with the highest activity towards VPA glucuronidation, were found to have little influence on VPA pharmacokinetics in healthy subjects [6]. However, because of the small sample size (14 subjects), the authors themselves were somewhat uncertain about the exact influence of UGT2B7 polymorphisms on VPA pharmacokinetics. Our results, based on the analysis of 136 epilepsy patients

Table 2 Statistical analysis of UGT1A3 allele frequencies among different populations

Allele	Frequency in epilepsy patients	Frequency in normal Chinese population	Frequency in general Japanese population	Frequency in general Caucasian population
UGT1A3	n=242	n=250[b]	n=200[c]	n=162[d]
*1	0.42	0.68*	0.61*	0.35*
*2a	-	0.01	-	0.58
*2b	0.21	0.09*	0.13*	-
*3a	-[a]	0.05	-	0.07
*3b	0.18	0.07*	0.10*	-
*4	0.05	0.06	0.11*	-
*5	0.07	0.04	0.06	-

*p<0.05, compared with Chinese epileptic patients by chi-square test

[a] -, Not detected in epilepsy patients or no published data currently available for other populations

[b] Based on data reported by Chen et al. [18]

[c] Based on data reported by Iwai et al. [24]

[d] Based on data reported by Lampe et al. [25]

Table 3 Statistical analysis of UGT1A6 and UGT2B7 genotype frequencies among different populations

Genotype	Frequency in epilepsy patients	Frequency in normal Chinese population	Frequency in general Japanese population	Frequency in general Caucasian population
UGT1A6	n=242	n=534[a]	n=195[c]	n = 100[e]
541AA	0.65	0.60	0.62	0.46 *
541AG	0.33	0.35	0.33	0.43
541GG	0.02	0.04	0.05	0.11*
UGT1A6	n =242	n=534[a]		n = 245[f]
552AA	0.57	0.57	-[d]	0.48*
552 AC	0.39	0.37	-	0.42
552CC	0.04	0.06	-	0.10*
UGT2B7	n=242	n =218[b]	n=84[b]	n=91[b]
802CC	0.45	0.44	0.51*	0.28*
802CT	0.47	0.47	0.44*	0.47
802TT	0.08	0.09	0.05*	0.25*

*p<0.05, compared with Chinese epileptic patients by chi-square test

[d] -, Not detected in epilepsy patients or no published data currently available for other populations

[a] Based on data reported by Xing et al. [26]

[b] Based on data reported by Lin et al. [30]

[c] Based on data reported by Saeki et al. [27]

[d] -, Not detected in epilepsy patients or no published data currently available for other populations

[e] Based on data reported by Lampe et al. [28]

[f] Based on data reported by Menard et al. [29]

Table 4 Influence of UGT1A3 genotypes on plasma valproic acid (VPA) C_S[a] in epilepsy patients receiving VPA monotherapy[b]

Genotype	Sample (*n*)	VPA C_S (μg·kg·mL^{-1}·mg^{-1})
UGT1A3	*n* = 128	
*1/*1	58	4.68±1.24
*1/*2b	19	4.74±1.32
*2b/*2b	5	4.92±0.64
*1/*3b	21	4.79±1.34
*3b /*3b	2	5.44(2.08-8.80)
*1/*4	7	4.80±2.30
*1/*5	12	3.30±0.99*
*5/*5	4	3.12±1.09*
Statistics		15.518, *df*=8, *P* <0.01

*P<0.05, compared with wild type *1/*1

Data are presented as the mean ± standard deviation (SD). Data were preferentially examined using the nonparametric Kruskal-Wallis test and then by one-way analysis of variance (ANOVA) post hoc test

[a] Standardized plasma trough concentration [trough plasma concentration/(dairy dose/weight)]

[b] Of 136 patients receiving VPA monotherapy, 128 carried UGT1A3 variants identified in this study

receiving VPA monotherapy, may lead to a more definitive conclusion that UGT2B7 polymorphism exerts little influence on the steady-state plasma concentration of VPA. A previous study using recombinant UGT1A6 variant enzymes found that the UGT1A6*2 allele possessed a two-fold higher activity than the wild type towards VPA glucuronidation [14]. However, we found that the genetic

Table 5 Influence of UGT1A6 and UGT2B7 genotypes on plasma VPA C_S in the epilepsy patients receiving VPA monotherapy

Genotype	Sample (*n*=136)	VPA C_S (μg·kg·mL^{-1}·mg^{-1})
UGT1A6 A541G		
AA	88	4.52±1.38
AG	45	4.60±1.58
GG	3	5.92±2.72
Statistics		0.958, *df*=2, *P*=0.619
UGT1A6 A552C		
AA	83	4.55±1.45
AC	50	4.61±1.55
CC	3	4.82±1.75
Statistics		0.158, *df*=1, *P* =0.691
UGT2B7 C802T		
CC	65	4.81±1.58
CT	60	4.27±1.25
TT	11	4.84±1.89
Statistics		4.687, *df*=2, *P* =0.096

Data are presented as the mean ± SD and were examined using the nonparametric Kruskal-Wallis test

Table 6 Influence of UGT1A3, UGT1A6, and UGT2B7 genotypes on carbamazepine–VPA interactions[a]

Genotype	Sample (*n*)	VPA C_{ST} (μg·kg·mL^{-1}·mg^{-1})
UGT1A3	36	
*1	18	3.39±1.49
*2b	7	3.53±0.70
*3b	8	3.24±1.17
*4	-	-
*5	3	3.08±0.94
UGT1A6 A541G	38	
AA	16	3.54±0.68
AG	22	3.18±1.46
UGT1A6 A552C	38	
AA	19	3.42±1.11
AG	19	3.25±1.29
UGT2B7 C802T	38	
CC	13	3.26±1.54
CT	25	3.38±1.01

Data are presented as the mean ± SD and were examined by the one-way ANOVA post hoc test

[a] Of 38 patients co-administered with carbamazepine and VPA, 36 carried UGT1A3 variants identified in this study

polymorphism of UGT1A6 had no influence on the VPA pharmacokinetics in Chinese epilepsy patients. Such an inconsistency may be explained by poor in vitro to in vivo correlations that have been observed in multiple genotype–phenotype association studies on UGTs.

Allelic distributions of UGT1A3 vary to a significant extent in different racial populations, especially between Asians and Caucasians [15, 18, 24, 25]. Our study further verified the differential racial distribution of various UGT1A3 polymorphisms. It was of interest to find that the UGT1A3 allelic distribution in our Chinese epilepy patients varies significantly from that in Chinese healthy subjects (Table 2); the functional significance of this difference may warrant further research to explore whether or not the UGT1A3 polymorphism is a genetic determinant of epileptic susceptibility.

Our genotype and phenotype association analysis showed that our Chinese epilepsy patients with the UGT1A3 A17G polymorphism and UGT1A3*5 allele were characterized with a significant lower VPA C_S. This result seems to be inconsistent with those from previous reports where the UGT1A3*5 variant was found to be associated with a slightly lower activity (86%) than the wild type towards the metabolism of its typical substrate estrogen [24]. However, previous reports on the enzyme activities of different UGT1A3 variants were largely controversial. For example, in one study the UGT1A3*2 allele was identified with a 3.7-fold higher intrinsic clearance than the wild type towards the

metabolism of estrone, whereas in another study the authors reported a moderate lower activity of this allele. There is still no information available on the activity of UGT1A3 variants in metabolizing VPA; thus, it is difficult to conclude that the lower plasma concentration of VPA in the UGT1A3*5 carriers is caused by the increased enzyme activity of this variant. In addition, previous reports on the influence of the UGT1A3 polymorphism on its transcription and protein expression were also quite controversial. In one study, UGT1A3*2 was found to be closely associated with a 7.3-fold increase in the protein expression of UGT1A3 in the human liver [19]; in contrast, an analysis using reporter gene transfection in Hepg2 cells revealed a 60% lower transcriptional activity of UGT1A3*2[15]. Therefore, much work remains to be done to determine the detailed enzymatic properties of various UGT1A3 variants, including UGT1A3*5, a potential genetic determinant of VPA pharmacokinetics.

The co-medication of drugs, such as carbamazepine, is another important determinant of the inter-individual pharmacokinetic variability of VPA [36]. Taking into account that the genetic polymorphisms of UGTs may influence drug–drug interactions [37, 38], we sub-grouped the patients co-medicated with carbamazepine based on their UGT genotypes to determine the possible influence of UGT polymorphisms on carbamazepine–VPA interactions. Our results showed no significant difference among the differently genotyped subgroups, suggesting that the carbamazepine–VPA pharmacokinetic interaction might not be influenced by UGT genotype.

In conclusion, our results demonstrate that the genotype distribution of UGT1A3 in a population of Chinese epilepsy patients was significant different from that in Chinese healthy subjects. Based on a detailed genotype-to-phenotype assay of all three major UGT isozymes involved in VPA metabolism, including UGT1A3, UGT1A6, and UGT2B7, we found that only UGT1A3*5 is a potential genetic determinant leading to the reduced plasma levels of VPA in our Chinese epilepsy patients. The results obtained from this study suggest that it may be necessary to increase VPA dose for UGT1A3*5 carriers to maintain its therapeutic range of 50–100 μg/mL.

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