Analysis Of Influencing Factors Of Plasma Concentration Of Oxcarbazepine Monotherapy In Children With Epilepsy

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Research Article

Keywords: Children with epilepsy, Oxcarbazepine, Genetic polymorphism, Plasma concentratio

Posted Date: March 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1432957/v1

Abstract

Purpose: The aim of this study was to investigate the factors affecting the plasma concentration of oxcarbazepine (OXC) monotherapy in children with epilepsy.

Methods: We recruited 125 children with epilepsy who received OXC monotherapy. 27 single nucleotide polymorphisms were detected by MassARRAY genotyping technology to evaluate the influence of related factors on the plasma concentration of OXC monotherapy. The plasma concentration of 10-hydroxycarbamazepine (MHD), the main active metabolite of OXC, was determined by high performance liquid chromatography (HPLC).

Results: The weight was found to be associated with concentration-dose ratio and maintenance dose. The duration of seizure was found to be associated with concentration-dose ratio. Carriers of the UGT1A4 rs2011425 mutant allele A or G had higher MHD plasma concentration than wild homozygous TT type. Carriers of the UGT2B15 rs1902023 mutant allele C had higher plasma concentration than wild homozygous AA types. The concentration-dose ratio of patients with ABCB1 rs1045642 mutation homozygous GG type is higher than heterozygous AG type. The concentration-dose ratio of patients with CACNA1H rs2753325 heterozygous AG type was higher than mutant homozygous GG type. We established a concentration prediction equation for OXC monotherapy in children with epilepsy.

Conclusion: This study clarified the association of weight, duration of seizure, and gene polymorphisms of UGT1A4 rs2011425, UGT2B15 rs1902023, ABCB1 rs1045642 and CACNA1H rs2753325 with MHD plasma concentration. The concentration prediction equation of OXC monotherapy in children with epilepsy was constructed, which provides a reference for individualized clinical administration.

Introduction

Epilepsy is a chronic brain disease characterized by recurrent, episodic and transient central nervous system dysfunction caused by abnormal firing of neurons in the brain. Epilepsy occurs in people of any age, region, and race, but it has a high incidence in children and adolescents, and is one of the common neurological diseases in pediatrics. Epidemiological studies in China showed that the incidence rate of epilepsy in children ranges from 41–187/100,000[1]. In children, the incidence is highest in the first year of life and declines to adult levels by the end of the first decade[2]. Epilepsy is a long-term and recurring disease that will seriously threaten the physical and mental health of patients. If not controlled reasonably and effectively, it will affect the cognitive function, intellectual development and quality of life of patients, especially in children. Therefore, reasonable and effective epilepsy treatment is of great significance to protect children's physical and intellectual development.

At present, epilepsy treatment is mainly based on drugs. Oxcarbazepine (OXC) is a second-generation anti-epileptic drug, which anti-epileptic mechanism is to stabilize neuronal cell membranes by blocking voltage-sensitive sodium channels and reducing voltage-activated neuronal calcium currents[3]. It can be used as first-line treatment of children with generalized and partial seizures with or without secondarily

generalized seizures[4]. OXC is a 10-ketone derivative of carbamazepine (CBZ), but their pharmacokinetics are significantly different, and the former is well tolerated and has few adverse reactions[5]. The main biotransformation product of OXC in humans is the biologically active metabolite monohydroxy carbamazepine (MHD), to which OXC is rapidly reduced by cytosolic enzymes in the liver[6]. There is only a small amount of OXC in human peripheral blood, and MHD is the main form of existence.

In the process of clinical application, it was found that there are wide individual differences in the OXC plasma concentration. Studies have found that individualized differences in OXC may be related to non-genetic factors such as age, gender, weight, and type of seizures, and may also be related to genetic polymorphisms. After oral administration, OXC is absorbed through the gastrointestinal tract, and then distributed to the brain tissue through the blood-brain barrier, while acting on the corresponding targets to exert anti-epileptic effects. Finally, it is cleared by the kidneys and excreted in the urine. This process involves genetic polymorphisms of various receptors and enzymes, which affect drug absorption, distribution, and metabolism, and ultimately lead to differences in drug concentrations. This study explored the relevant factors affecting the plasma concentration of OXC monotherapy in children with epilepsy, which can provide reference for clinical individualized drug administration and promote the rational use of the drug.

Methods

Subjects

This study included children with epilepsy who received OXC monotherapy from February 2019 to December 2019 in epileptic outpatients at the No. 900 Hospital of Joint Logistics Support Force of the PLA. The study was approved by the Ethical Committee of No. 900 Hospital of Joint Logistics Support Force of the PLA (Approval No. 2020-001). All procedures in this study were strictly based on the Declaration of Helsinki. Each participant or their legal guardian provided written informed consent.

Inclusion and exclusion criterias

Inclusion criterias

(1) Epilepsy was diagnosed according to International League Against Epilepsy(ILAE) 2017 diagnostic criteria for epilepsy and epilepsy syndrome, and the type of seizure was determined; (2) Age ≤ 14 years, gender is not limited; (3) The function of heart, liver, kidney and other important organs was normal, and there were no other diseases that affected the treatment of epilepsy; (4) Regular prescribed with OXC tablets or OXC oral suspension(trade name: Trileptal; manufacturer: Novartis Farma S.P.A) as monotherapy for > 1 month; (5) Good medication compliance, complete case data, can cooperate with follow-up.

Exclusion criterias

(1) Diagnosed as non-epileptic seizures, such as breath-holding seizures, false seizures, etc; (2) Patients with brain CT or MRI are showing progressive brain diseases, such as inflammation, tumor, etc; (3) Abnormal function of liver and kidney and other important organs; (4) Patients with developmental and metabolic disorders are receiving multiple treatments; (5) Incomplete case data, failure to follow up and complete the examination as required; (6) Withdraw from the study for other reasons.

Sample collection and determination of MHD concentration

After at least one month of continuous treatment with the same dose of OXC monotherapy, peripheral venous blood (4ml) was collected in ethylene diamine tetraacetic acid (EDTA) tube before morning administration to measure MHD trough concentration. MHD plasma concentration were determined by high performance liquid chromatography (HPLC). Due to significant differences in oral doses of patients, steady-state plasma concentration (Css) of MHD was adjusted by concentration-dose ratio (CDR), CDR = Css/maintenance dose. Maintenance dose was defined as the corresponding dose to the Css of OXC monotherapy for more than 1 month. OXC maintenance dose were adjusted by weight.

Genotyping

By reviewing literature and searching Pharm GKB (http://www.pharmgkb.org) website, we screened 27 single nucleotide polymorphisms (SNPs) that may be related to OXC plasma concentration, including CYP2C19*3 rs4986893, CYP2C19*2 rs4244285, CYP3A4 rs4646440, rs2242480, CYP3A5 rs15524, rs776746, UGT2B7 rs7439366, UGT1A9 rs2741049, UGT1A4 rs2011425, UGT1A6 rs6759892, UGT2B15 rs1902023, ABCB1 rs1045642, rs2032582, rs10234411, rs1128503, ABCC2 rs2273697, rs3740066, rs717620, SCN1A rs2298771, rs3812718, SCN2A rs2304016, rs17183814, CACNA1H rs61734410, rs2753326, rs2753325, rs2235634, CACNA1I rs3747178. Genomic DNA was extracted from whole blood samples by nucleic acid extraction and purification kit (Shanghai BaiO Technology Co.,Ltd). Samples were detected by the MassARRAY genotyping technique, and primers were designed using Agena company online primer design software --- Assay Design Suite v2. (https://seqpws1.agenacx.com/AssayDesignerSuite.html) (as shown in supplementary Table 1). The sequencing of PCR products was performed using MALDI-TOFMS analysis technology, and the results were genotyped by Typer 4.0 software (Agena Bioscience, CA, USA). Among the 125 patients, 27 SNPs were all successfully genotyped, with a success rate of 100%.

Statistical analysis

The measurement data conforming to normality are expressed as mean ± standard deviation ($\bar{x}\pm s$). Otherwise, the measurement data are expressed as median and quartile [M(P25-P75)]. The count data are expressed as frequency (%). The Hardy-Weinberg equilibrium (HWE) test was performed by $\chi 2$ test or fisher's exact test to evaluate the deviation of genotype frequencies. The comparison between measurement data is based on the normality test result. If normal distribution is followed, t-test or one-way ANOVA should be adopted; otherwise, non-parametric test should be adopted. Bivariate correlation analysis was used to investigate the correlation between MHD plasma concentration and OXC maintenance dose, as well as the measured concentration and predicted concentration. Pearson

correlation analysis was used for bivariables conforming to normal distribution, otherwise spearman correlation analysis was employed. The concentration prediction equation is established by the stepwise method of multiple linear regression. All data analyses were performed using SPSS (version 25.0, SPSS Inc., IL, USA). Statistical significance was accepted at two-side p-values < 0.05.

Results

Demographics and clinical characteristics of the children with epilepsy

Table 1 summarizes the demographic and clinical characteristics of patients in detail, including gender, age, height, weight, birth weight, whether natural birth, whether preterm birth, family history, suffocation history, whether the brain structure is normal, age of onset, duration of seizure, seizure type, etiology, OXC maintenance dose, MHD concentration, and CDR. A total of 125 children with epilepsy on OXC monotherapy were included (75 male, 50 female). The mean age of the sample was 8.93 ± 2.86 years old.

Table 1
Demographics and clinical data of the 125 children with epilepsy.

Demographics and clinical characteristics	data
Gender (Male/Female)	75(60.0%)/50(40.0%)
Age (years)	8.93 ± 2.86
Height (cm)	135.45 ± 19.43
Weight (kg)	31.70(25.45-40.00)
Birth weight (normal/abnormal)	116(92.8%)/9(7.2%)
Natural birth (yes/no)	81(64.8%)/44(35.2%)
Preterm birth (yes/no)	10(8.0%)/115(92.0%)
Family history (yes/no)	31(24.8%)/94(75.2%)
Suffocation history (yes/no)	12(9.6%)/113(90.4%)
Brain structure (normal/abnormal)	100(80.0%)/25(20.0%)
Age of onset (years)	5.74(2.43–8.35)
Duration of seizure (years)	0.48(0.08–2.46)
Seizure type (n, %)	
Simple partial seizures	8(6.4%)
Complex partial seizures	34(27.2%)
Partial secondarily generalized seizures	67(53.6%)
Generalized seizures	16(12.8%)
Etiology (n, %)	
Primary epilepsy	68(54.4%)
Secondary epilepsy	57(45.6%)
OXC maintenance dose (mg/kg/day)	13.64(10.00-19.47)
MHD concentration(μg/mL)	9.88(6.81–13.77)
CDR (μg•kg/mg/mL)	0.74 ± 0.27

Association between demographics and clinical characteristics and MHD plasma concentration

In assessing the effects of demographic and clinical characteristics on MHD plasma concentration, we found that weight was correlated with OXC maintenance dose and CDR, and duration of seizure was

correlated with CDR (as shown in Fig. 1 and supplementary Table 2). Patients with weight < 25 kg had higher OXC maintenance dose than those ≥ 35 kg [16.00(12.15–21.07) vs 11.82 (9.29–16.80), $P = 0.014$]. Patients with weight ≥ 35 kg had higher CDR than those weight < 25 kg [0.85 (0.65–0.98) vs 0.60 (0.50–0.77), $P = 0.001$] and weight between 25–35 kg [0.85 (0.65–0.98) vs 0.65 (0.55–0.80), $P = 0.020$]. Patients with duration of seizure ≥ 6 years had significantly higher CDR than those < 1 year (0.90 ± 0.36 vs 0.74 ± 0.26, $P = 0.028$), those between 1–3 year (0.90 ± 0.36 vs 0.64 ± 0.21, $P = 0.004$), and those between 3–6 year (0.90 ± 0.36 vs 0.69 ± 0.18, $P = 0.031$). There was a significant correlation between MHD plasma concentration and OXC maintenance dose ($r = 0.615$, $P = 0.000$; as shown in Fig. 2).

Association between gene polymorphism and MHD plasma concentration

Four of the 27 genotype frequencies were not consistent with HWE, including CYP3A5 rs15524, UGT1A4 rs2011425, ABCC2 rs717620, and CACNA1H rs2753326 (as shown in supplementary Table 3). Among the 27 tested SNPs, only UGT1A4 rs2011425 and UGT2B15 rs1902023 showed significant associations with MHD plasma concentration, and ABCB1 rs1045642 and CACNA1H rs2753325 were significantly correlated with CDR. However, we failed to detect any significant associations between genotypes and OXC maintenance dose (as shown in Fig. 3 and supplementary Table 4).

Mutant homozygous was not detected at UGT1A4 rs2011425, and the plasma concentration of MHD in patients with TA or TG genotypes was significantly higher than those with the TT genotypes [10.69(9.18–14.16) vs 8.79(6.27–12.66), $P = 0.037$]. Patients with the UGT2B15 rs1902023 AA genotypes had lower MHD concentration than those with the CC genotypes[10.74(9.33–14.71) vs 7.85(5.53–11.24), $P = 0.006$] and AC + CC genotypes [7.85(5.53–11.24) vs 10.49(7.94–14.19), $P = 0.003$]. Compared with CC genotypes, AA + CC genotypes of UGT2B15 rs1902023 was associated with lower MHD concentration [10.74(9.33–14.71) vs 7.85(5.53–11.24), $P = 0.006$]. The CDR in patients with the ABCB1 rs1045642 GG genotypes was significantly higher than those with the AG genotypes (0.79 ± 0.30 vs 0.68 ± 0.20, $P = 0.032$). Wild-type homozygous was not detected at CACNA1H rs2753325, and patients with AG genotypes had higher CDR than those with the GG genotypes (0.82 ± 0.27 vs 0.71 ± 0.26, $P = 0.044$).

The correlation between each factor and MHD plasma concentration was analyzed by multiple linear regression

Multivariate regression analysis was performed to evaluate the effects of weight, duration of seizure, OXC daily dose, UGT1A4 rs2011425, UGT2B15 rs1902023, ABCB1 rs1045642 and CACNA1H rs2753325 on the plasma concentration of MHD. After excluding irrelevant variables, weight, daily dose of OXC and UGT2B15 rs1902023 were included in the final regression equation (as shown in Table 2). These factors have significant statistical differences ($P < 0.05$). Finally, the obtained concentration prediction equation is C = 5.191 + 0.014*daily dose-1.818*weight + 0.912*UGT2B15 rs1902023 (weight < 25 kg is set as 0,

25–35 kg is set as 1, and ≥ 35 kg is set as 2; UGT2B15 rs1902023 AA type is set as 0, AC type is set as 1, CC type is set as 2).

The above equation was used to predict the plasma concentration of MHD in patients. Correlation analysis was conducted between predicted concentration and measured concentration of all patients, and the conclusion was statistically significant (r = 0.610, *P* = 0.000; as shown in Fig. 4).

Table 2
The results of multiple linear regression analysis of MHD concentration.

Covariate	Unstandardized coefficients		Standardized coefficients	t value	*P* value
	B	Std. Error	Beta		
constant	5.191	0.848		6.122	0.000*
OXC daily dose (mg)	0.014	0.002	0.684	8.919	0.000*
Weight (kg)	-1.818	0.461	-0.301	-3.946	0.000*
UGT2B15 rs1902023	0.912	0.410	0.154	2.224	0.028*
**P* < 0.05 was statistically significant					

Discussion

This study found that within a certain dose range of 8–46 mg/kg, the MHD plasma concentration was positively correlated with the maintenance dose of OXC, which was consistent with previously reported literature [7, 8]. The Perucca's study[7] showed that MHD plasma concentrations in children are considerably lower than those adults receiving comparable OXC dosages, possibly due to lower body fat/lean mass ratio, higher total body water, higher plasma protein binding rate, and higher renal blood flow in children.Other study has shown that children younger than 8 years have clearance rates 30–40% higher than those in older children[9]. As a result, children, especially younger children, need to be given more dosage to achieve the same plasma concentration. There were not many studies on the correlation between gender and age with MHD plasma concentration, and the conclusions were also different. In the previous study, the MHD plasma concentration increased with patient age[10]. Another study in the Korean population found that there are not associations between OXC concentration and patient age, weight, gender, or seizure type[11]. Partially consistent with previous studies, we only found that CDR increased with patient weight, and corresponding maintenance dose decreased with patient weight. This suggests that the pharmacokinetic behavior of MHD is weight-dependent, and its clearance rate tends to decrease with the increase of weight, which can be further explored. In terms of the duraton of epilepsy, it was found that the CDR in the ≥ 6 years group was significantly higher than that in the < 1 year group, 1–3 years group and 3–6 years group. The possible reason is that the age of the children in the disease

course ≥ 6 years group is relatively older, and the renal clearance rate is relatively lower, resulting in higher concentration.

The UDP-glucuronosyltransferase (UGT) superfamily participates in the glucuronidation metabolism of various endogenous substances and exogenous compounds[12]. The elimination of OXC and MHD is mainly by binding with UGT enzyme to form glucuronic acid conjugate, which is then excreted in the urine. In our study, of the four SNPs (UGT1A4 rs2011425, UGT1A6 rs6759892, UGT1A9 rs2741049 and UGT2B15 rs1902023), we found UGT1A4 rs2011425 and UGT2B15 rs1902023 were significantly associated with MHD plasma concentretion, which was inconsistent with Lu et al's study[13], as MHD plasma concentration of UGT1A9 rs2741049 mutant allele T carriers was significantly lower than those non-carriers. It may be explained by differences in the age of the population, because Lu et al included both children and adults in their study. In the pediatric population, smaller variation in microsomal glucuronidation activity was observed compared with that in adults, and the activities of UGT1A4, UGT1A6, UGT1A9 and UGT2B15 increased with age[14]. The human UGT1A4 gene is primarily expressed in the human liver, both in the biliary epithelium and the hepatocyte. In contrast to other UGT1A proteins, the catalytic activity of UGT1A4 is most specific for primary and secondary amines, sapogenins, as well as for steroid hormones, which are commonly present in therapeutic drugs[15]. At present, a large number of studies have reported that the variation of UGT1A4 rs2011425 is related to lamotrigine metabolism[16–18]. Reimers et al's study[18] found that the influence trend of UGT1A4 rs2011425 on enzyme activity depended on substrate type. For LTG glucuronidation, UGT1A4 rs2011425 variant showed reduction in activity as compared with the wild-type enzyme. Theoretically, UGT1A4 rs2011425 mutant LTG plasma concentration was higher than those wild-type. In this study, it was found that the UGT1A4 rs2011425 mutant allele carriers had higher plasma concentration, and whether OXC had the same influence trend on mutant enzyme activity as lamotrigine remains to be further studied. UGT2B15 was identified as important for the glucuronidation of androgenic steroids, drugs, drug metabolites and other xenobiotic[19]. The mutant allele of UGT2B15rs1902023 was found to reduce the systemic clearance of lorazepam, while also reducing the glucuronidation level of oxazepam in the liver, suggesting that the mutant allele carriers had a relatively higher plasma concentration[20]. Consistent with the above research, we found that the carriers of the variant allele of UGT2B15rs1902023 had higher MHD plasma concentration than homozygous wild-type. As for UGT2B7 rs7439366, the allele frequency of the nonsynonymous polymorphism in the Chinese population is 32.8%[21]. Our study demonstrated that UGT2B7 rs7439366 gene polymorphism was not correlated with MHD plasma concentration, which was in agreement with Shen et al's study[22] and Ma et al's study[23].

Cytochrome P450 (CYP450) system is a major group of biotransformational enzymes in many organisms, including humans, and is used for the metabolism of endogenous and exogenous compounds[24]. OXC metabolism is largely unaffected by CYP450 system. However, OXC can inhibit CYP2C19 and induce CYP3A4/5. At present, studies on the influence of CYP450 gene polymorphism on MHD plasma concentration are as follows: CYP3A4 rs4646440, CYP3A4 rs2242480, CYP3A5 rs15524, CYP3A5 rs776746, CYP2C19*2 rs4244285 and CYP2C19*3 rs4986893[25–27]. In this study, no correlation was found between the polymorphisms of the above genes and MHD plasma concentration,

which was inconsistent with Zhou et al's study[25], who considered that the plasma concentration of patients carrying CYP2C19*3 mutant allele was higher. The most characterized alleles of the CYP2C19 are CYP2C19*2 and CYP2C19*3, and CYP2C19*2 is the most common allele among Asians[28]. CYP2C19 is responsible for catalytic oxidation and metabolic clearance of up to 20% of clinically important antiepileptic drugs, such as phenobarbital and phenytoin[29]. However, previous study suggested that there was no statistical difference in the antiepileptic drug inhibition effect between CYP2C19*2 and CYP2C19*3 genotypes[30].

In addition to the effects of the above metabolic enzymes, new progress has been made in recent years on the effect of transporter (ABCB1, ABCC2 coding) related gene polymorphism on the plasma concentration of MHD. The ABCB1 gene encodes a highly polymorphic P-gp. ABCB1 rs1045642 in exon 26 is the most widely studied SNP. According to the current research, we have concluded that P-gp is involved in the transport of OXC and MHD at the blood-brain barrier, which means that they are the substrates of P-gp[31, 32]. A study found[22] that ABCB1 rs1045642 gene polymorphism was significantly associated with CDR, and CDR of CC genotype was higher than that of CT and TT genotype, which was consistent with our results. However, another study[26] involving 40 Chinese patients with epilepsy found no correlation between ABCB1 (rs1045642, rs2032582, rs1128503 and rs10234411) and the CDR. In addition, ABCC2 is also a member of the ATP binding cassette transporter superfamily. The overexpression of ABCC2 transporters on the blood-brain barrier cells will increase the outflow of AEDs into the capillary cavity, which ultimately leads to a reduction of AEDs concentration in the brain that is insufficient to control seizures[33]. In vitro studies indicated that CBZ is a substrate of ABCC2[34], and the change of ABCC2 function will affect the absorption and excretion of its substrate. OXC is a 10-ketone analogue of CBZ, and whether ABCC2 affects the maintenance dose and plasma concentration of OXC needs to be further studied. Our study failed to observe a significant correlation among ABCC2 rs3740066 and ABCC2 rs2273697 and MHD plasma concentration, which was consistent with previous studies[22, 23]. However, Ma et al's study[23] found that carriers of the ABCC2 rs2273697 variant alleles required significantly higher OXC maintenance doses than non-carriers.

OXC plays an antiepileptic role by the inhibition of sodium channel activity. Sodium channels consist of one large α-subunit and two small β-subunits[35]. Variants in four isoforms of the α-subunit, Nav1.1, Nav1.2, Nav1.3,and Nav1.6 (encoded by the SCN1A, SCN2A, SCN3A and SCN8A genes, respectively), have been associated with epilepsy[36]. The association of SCN1A and SCN2A polymorphisms with MHD plasma concentration and OXC maintenance dose has been discussed in several studies. In a study on Chinese Han patients with epilepsy[23], of the four candidate alleles (SCN1A rs3812718, SCN1A rs2298771, SCN2A rs17183814 and SCN2A rs2304016), only SCN1A rs3812718 was significantly associated with OXC maintenance dose and CDR, which was inconsistent with the Italian populations[37]. It may be explained by differences in ethnic inclusion. Another study[38] found that the SCN2A rs17183814 mutant required a lower OXC maintenance dose and higher CDR in the over-weight group, while higher OXC maintenance dose in the low-weight group. In this study, we failed to observe a significant correlation among SCN1A/SCN2A genotypes and OXC maintenance dose and MHD plasma concentration.

The voltage-dependent calcium channel is composed of "α1", "β", "α2δ" and "γ" subunits, in which "α1" is the functional subunit and "β", "α2δ" and "γ" are the auxiliary subunits[39]. According to different pharmacological characteristics, voltage-dependent calcium channels can be divided into P/Q-type (conducted by Cav2.1 channel, which is encoded by the CACNA1A genes), N-type (conducted by Cav2.2 channel, which is encoded by the CACNA1B genes), R-type (conducted by Cav2.3 channel, which is encoded by the CACNA1E genes), L-type (conducted by Cav1.1-1.4 channels, which is encoded by the CACNA1S, CACNA1C, CACNA1D and CACNA1F genes, respectively) and T-type (conducted by Cav3.1-3.3 channels, which is encoded by the CACNA1G, CACNA1H and CACNA1I genes, respectively)[40]. In a previous study[41], minor allele of two polymorphisms (CACNA1H rs61734410, CACNA1I rs3747178) in the ethosuximide subjects were more common in not seizure free participants, and two CACNA1H polymorphisms (rs2753326, rs2753325) in the lamotrigine subjects appeared more commonly among seizure free participants, and one polymorphism of CACNA1H rs2235634 in the valproic acid subjects was associated with increased rates of not seizure free outcomes. Whether this correlation also exists in OXC requires further study. In our study, we discussed five polymorphisms of CACNA1H and CACNA1I, and it was found that the CDR of CACNA1H rs2753325 heterozygous AG type was significantly higher than mutant homozygous GG type, suggesting that the gene polymorphism of calcium channel may be related to OXC maintenance dose and MHD plasma concentration.

Conclusion

The present study comprehensively investigated the effects of demographic characteristics, clinical characteristics and gene polymorphisms in pharmacokinetic and pharmacodynamic pathways on OXC plasma concentration in children with epilepsy, and for the first time explored the effects of calcium channel gene polymorphisms on OXC plasma concentration. Of course, there are also some shortcomings in this study. Due to the limitation of the subject time, the follow-up time of the clinical efficacy of the cases is not long enough and the sample size is small. We will continue to follow up this study in the future, and expand the collection of patients, while prolonging the study time.

Declarations

Acknowledgments We sincerely thank the medical staff from Epilepsy Clinic, No. 900 Hospital of Joint Logistics Support Force of the PLA, for their help and collaboration in the present study.

Author contribution Concept and design: all authors. Acquisition, analysis or interpretation of data: Nannan Yao, Shan Huang. Drafting of the manuscript: Nannan Yao. Critical revision of the manuscript for important intellectual content: Hongtao Song, Aiwen Huang.

Funding This work was supported by the In-hospital project of the No. 900 Hospital of Joint Logistics Support Force of the PLA (2019L16).

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval The study protocol was approved by the Ethics Committee of the No. 900 Hospital of Joint Logistics Support Force of the PLA (Approval No. 2020-001). The study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

Consent to publish Informed consent was obtained from the parents or legal guardians of all individual participants in this study.

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Figures

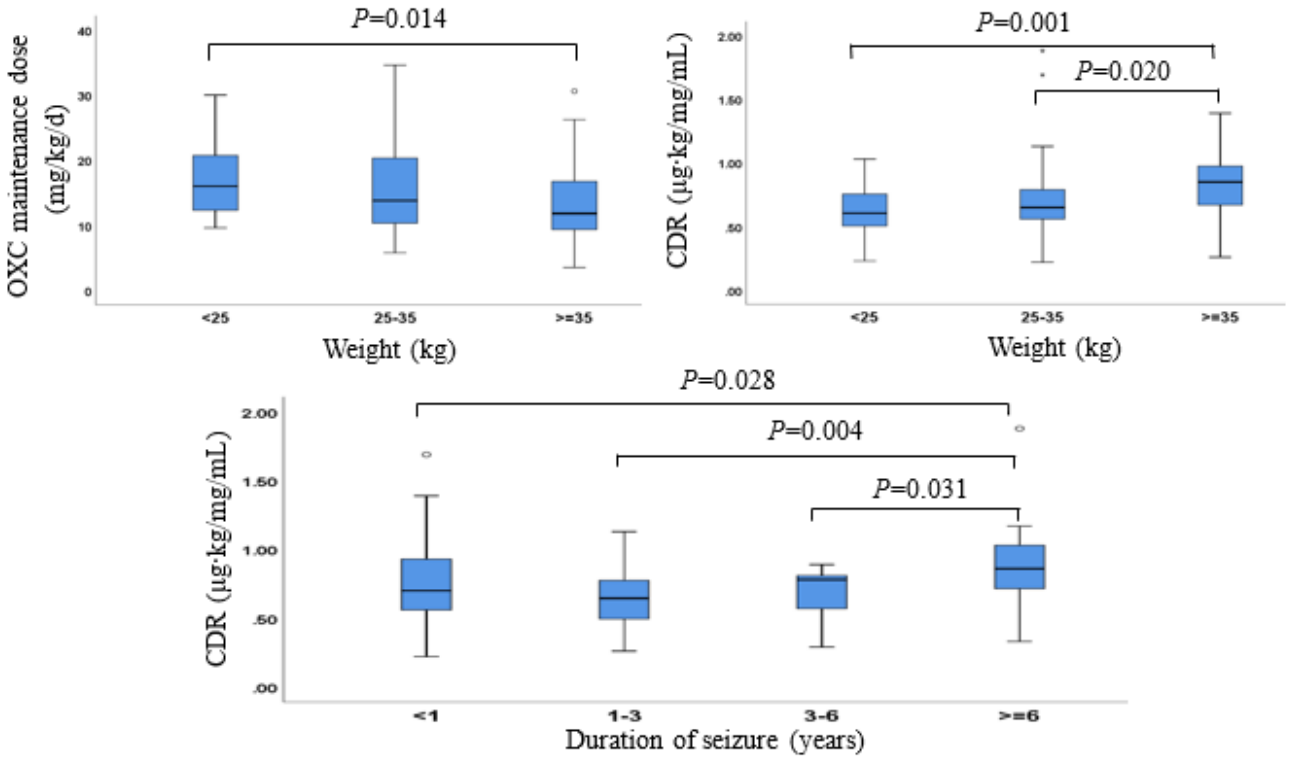

Figure 1

Correlation of demographic and clinical data with OXC maintenance dose and CDR. Weight was related to OXC maintenance dose and CDR, and disease course was related to CDR.

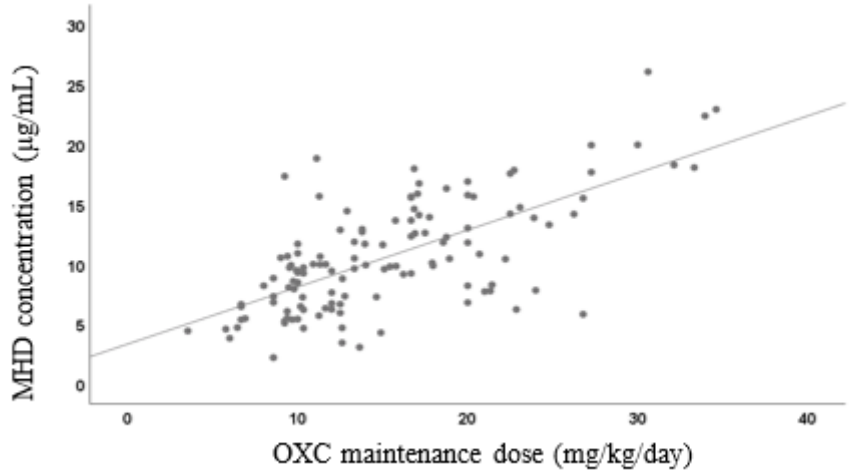

Figure 2

The association of OXC maintenance dose with MHD concentration.

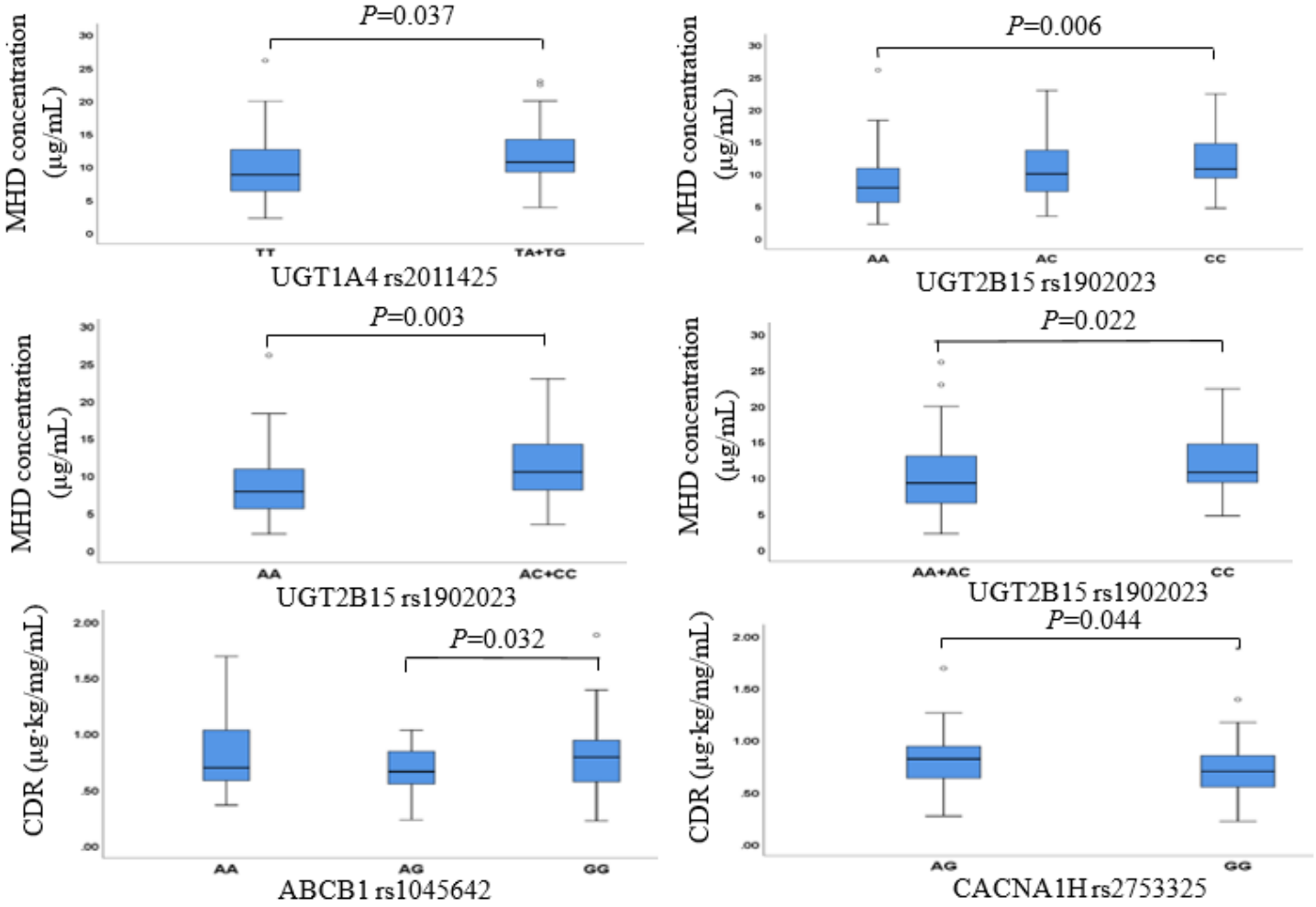

Figure 3

The association of UGT1A4 rs2011425 and UGT2B15 rs1902023 genotype with MHD concentration. The association of ABCB1 rs1045642 and CACNA1H rs2753325 genotype with CDR.

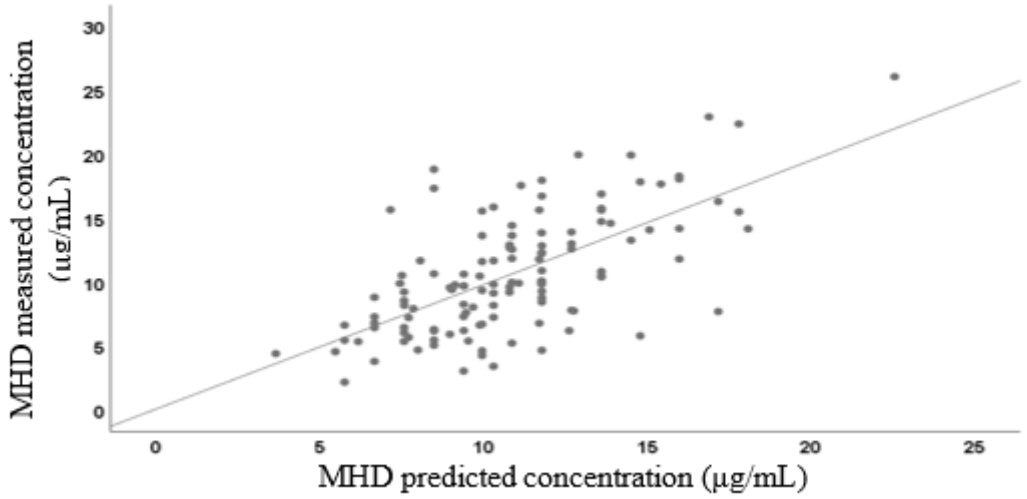

Figure 4

The association of MHD predicted concentration with MHD measured concentration.

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