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Influence of age and co-medication on the concentration and efficacy of valproic acid in Chinese epilepsy children

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Abstract: Valproic acid (VPA) was a classic antiepileptic drug for fifty years. However, individual variability of plasma drug concentration was obvious in epilepsy patients and few researches focused on the relationship between concentration and efficacy. Consequently, in this study, the correlation of VPA concentration and efficacy was analyzed according to the subgroups of age, gender, and co-medication in Chinese children. Children diagnosed by epilepsy with monitoring of VPA from April 1, 2014 to March 31, 2017 were recruited. Data on age, gender, diagnosis, dose, co-medication, and concentration of VPA was collected and analyzed according to the efficacy. Total of 486 concentration data was included in this study. Doses and plasma concentrations were significantly increased with age (P<0.001, P<0.001). After adjusted by dose, the uncontrolled elder children (12-18 years) showed higher concentration/dose (C/D) ratio than the controlled group (P=0.02). However, there were no differences between male and female. For polytherapy, the C/D ratio of uncontrolled-group was higher than that of controlled group (P=0.005), especially with levetiracetam (LEV) and topiramate (TPM) (P=0.028, P=0.048). Age could explain some of the inter-individual pharmacokinetic of VPA, however, gender was not related to the concentration or efficacy of VPA which suggested that concentration monitoring was indispensable to children. Low metabolism, especially in the combination of LEV and TPM, might associate with the resistance of VPA, which could be a new sight to explore the resistance of VPA.

Keywords: Age, co-medication, concentration, efficacy, valproic acid.

INTRODUCTION

Valproic acid (VPA) is a classic antiepileptic drug for fifty years by virtue of the wide scope effect and kind tolerance (Rakitin *et al*., 2015). It is advised as the first line of therapy for epilepsy by the current National Institute for Health and Care Excellence guidelines. Previous researches have shown that it still is the most commonly used antiepileptic drugs (AEDs) in many countries such as India, Singapore and Netherland (Bhatt *et al*., 2014; Hasan *et al*., 2010; van de Vrie-Hoekstra *et al*., 2008).

VPA with a higher percentage of serum protein binding rates (90%) shows nonlinear pharmacokinetics and the biotransformation consists of three major metabolic pathways, including Uri dine diphosphate glucurono syltransferase (UGT) enzyme pathway, mitochondria β-oxidation way and cytochrome P450 (CYP) pathway, accounting for 50%, 40%, and 10%, respectively, which may lead to its widely individual variability in epilepsy patients (Dickinson *et al*., 1989). To verify the efficacy and monitor adverse effects, a concentration range from 50 to 100μg/ml was recommended by the International League against Epilepsy (ILAE) (Patsalos *et al*., 2008). However, the recommended concentration do not reflect the individual efficacy completely.

Clinical practice has showed that there are many children administered by VPA for long-time treatment but got inefficiency (Fernando-Dongas *et al*., 2000). Especially, resistance to VPA have a specificity of 100% to identify patients with drug resistance and correlated strongly with the bad social outcome (Gesche *et al*., 2017). However, the mechanism is still unclear. Previous study demonstrated that age at onset of absences, diagnosis, and onset of therapy were correlated to VPA response (Ollivier *et al*., 2009). Our previous study has illustrated that with the amount of AEDs added, the frequency, and dosage of VPA increased (Wang and Li, 2016). However, whether the plasma VPA concentrations were increased with doses and correlated to the effectiveness of VPA were undefined.

The purpose of this study was to explore the effects of age, gender and co-medication on the concentration and efficacy of VPA in Chinese children.

MATERIALS AND METHODS

Study population

This observational, single-center, retrospective study was performed by the therapeutic drug monitoring and treatment database of Children's Hospital of Fudan University from April 1, 2014 to March 31, 2017. Children aged from 0-18 years and administered by VPA at least one year were recruited. Medical charts on data of age, gender, diagnosis, dosage, and co-medication drugs including oxcarbazepine (OXC), lamotrigine (LTG), topiramate (TMP), levetiracetam (LEV) were collected

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from clinical examination records.

VPA monitoring

Serum was collected in the morning before VPA administration to detect the plasma concentration by direct chemiluminescence assay with Viva-E equipment (Siemens), with a linear range of 26.8-150μg/ml. Concentration-dose (C/D) ratio was used as previous research which expressed as plasma concentration / daily dose (JACKSON *et al*., 2015).

Groups

The plasma VPA concentrations were separated into three groups, the sub therapeutic (<50μg/ml), therapeutic (50-100μg/ml) and supratherapeutic concentrations (>100μg/ml) groups according to ILAE. Age was departed into five groups: 0-12 months, 13-24 months, 2-5 years, 6-11 years and 12-18 years based on the definition of the National Institute of Child Health and Human Development Pediatric Terminology released in July 2011(Williams *et al*., 2012).

Ones in a complete disappearance of seizure or continued to experience seizures during VPA treatment for more than half a year were classified into controlled- and uncontrolled-group.

STATISTICAL ANALYSIS

The rate of demographic data was divided by total patients (486) and the differences were analyzed through the χ^2 test. Values including dose, plasma concentration, and C/D ratio were expressed as Mean ± SE. One-way ANOVA was used for more than two groups while Students' T-test was utilized for two groups. Difference was considered statistically significant at $P<0.05$.

RESULTS

Demographic characteristics of 486 children

A total of 486 VPA concentrations from 335 children were enrolled in this study. Of which, 206 were well controlled while 129 were uncontrolled. There was a significant discrepancy on the distribution of age between the controlled and uncontrolled group. Children aged from 2 to 5 years were the most common seen in the uncontrolled group. However, no difference was found between male and female. Polytherapy was commonly applied in the uncontrolled group (table 1).

The association of VPA efficacy with concentration on the subgroup of age

The plasma VPA concentration widely varied from 29.0 to 179.6μg/mL (fig. 1). In total, doses and plasma concentrations significantly increased with ages ($P<0.001$, $P<0.001$), however, the C/D ratio was decreased ($P<0.001$). Uncontrolled children who elder than 6years required a higher dose than controlled patients, however, no significant difference was found in the concentration. After adjusted by dose, C/D ratio of uncontrolled children aged from 12to18 years was significantly higher than that in the controlled patients (table 2).

The association of VPA efficacy with concentration between male and female

In general, the ratio of male to female was 1.79 (table 1). Higher dose tended to be administered to male when compared with female ($P=0.029$) however no statistical difference between the plasma concentrations and C/D ratio was found. There was no discrepancy on dose, concentration and C/D ratio between controlled and uncontrolled group both in male and female table 3).

The association of VPA efficacy with concentration on monotherapy and polytherapy

In total, more doses were administered in polytherapy group than in monotherapy ($P=0.003$). However, there were no differences in dose and plasma concentrations of uncontrolled children between monotherapy and polytherapy. In controlled pediatric patients, higher doses were tended to administer in polytherapy than monotherapy but it got similar concentration, consequently, lower C/D ratio was revealed in polytherapy. Furthermore, the C/D ratio of controlled patients with polytherapy was significantly lower than that in the uncontrolled children, which suggested that resistant children might own slow metabolism, compared with responsive patients ($P=0.0054$) (table 4).

Effects of individual AEDs on C/D ratio and efficacy of VPA

To explore whether individual AEDs administered with VPA could disrupt the above results, the C/D ratio of individual AEDs was analyzed. Results showed that no obvious differences on the C/D ratio were found in co-administration with LTG, OXC, LEV and TPM. However, uncontrolled children had a significant increase C/D ratio than the controlled group when combined with LEV and TPM, which suggested that LEV and TPM might influence the metabolism of VPA in the resistant children and might be related to the efficacy ($P=0.028$, $P=0.048$) (fig. 2).

DISCUSSION

The variability of VPA was widely spread in Chinese epilepsy children. The percentage of plasma VPA concentration below, within, and above the reference range was 15.2%, 63.2% and 21.6%, respectively, which agreed to the results of Charfi R (Cherfi *et al*., 2015). However, no difference was found in the frequency between controlled and uncontrolled group ($\chi^2=1.9$, $P=0.38$). Furthermore gender did not relate to the VPA plasma concentration and efficacy. However, it was

Table 1: Demographic characteristics of 486 children

		Total		Controlled-		Uncontrolled-		χ^2, *P*-value
		No.	Percentage (%)	No.	Percentage (%)	No.	Percentage (%)	
Age	0-12 month	3	0.6	1	0.3	2	1.1	14.4, 0.006
	13-24 month	19	3.9	8	2.7	11	5.9	
	2-5 years	238	48.9	133	44.3	105	56.5	
	6-11 years	194	39.9	137	45.7	57	30.6	
	12-18 years	32	6.6	21	7.0	11	5.9	
Gender	Male	312	64.2	193	65.6	119	64.0	0.001, 0.98
	Female	174	35.8	101	34.4	67	36.0	
Co-medication	Monotherapy	254	52.2	192	63.8	62	33.3	42.7, <0.001
	Polytherapy	232	47.7	108	36.2	123	66.7	
	LTG	38	7.8	21	4.3	17	3.5	
	OXC	61	12.6	32	6.6	29	6.0	
	LEV	82	16.9	37	7.6	45	9.3	
	TPM	70	14.4	23	4.7	47	9.7	

Table 2: Difference between controlled- and uncontrolled-groups on dose, plasma concentration and C/D ratio in the subgroup of age

Dose/concentration/ratio	Age	Total	Controlled-	Uncontrolled-	*P*-value
Dose (g)					
	0-12 month	0.19±0.03	0.16	0.29±0.04	----
	13-24 month	0.32±0.02	0.32±0.04	0.31±0.08	0.90
	2-5 years	0.42±0.01	0.42±0.01	0.44±0.01	0.20
	6-11 years	0.65±0.01	0.63±0.01	0.70±0.03	0.04
	12-18 years	0.75±0.04	0.67±0.05	0.92±0.05	0.003
	P-value	<0.001	<0.001	<0.001	
Plasma concentration (μg/ml)					
	0-12 month	48.9±8.9	31.1	57.8±0.5	----
	13-24 month	62.5±5.1	54.6±4.3	68.3±8.0	0.20
	2-5 years	69.2±1.5	65.5±1.7	73.9±2.5	0.005
	6-11 years	88.4±2.1	86.1±2.4	93.9±3.9	0.09
	12-18 years	99.8±4.5	98.7±5.4	92.1±8.5	0.86
	P-value	<0.001	<0.001	<0.001	
C/D ratio [μg/(ml·g)]					
	0-12 month	265.1±48.6	194.4	300.5±57.6	----
	13-24 month	204.3±16.3	187.2±26.2	216.6±21.1	0.39
	2-5 years	173.4±4.8	166.3±5.6	182.5±8.3	0.10
	6-11 years	143.2±4.0	142.8±4.9	144.2±7.1	0.87
	12-18 years	127.2±8.2	140.3±10.2	162.2±11.2	0.02
	P-value	<0.001	0.008	<0.001	

Table 3: Difference between controlled- and uncontrolled-groups on dose, plasma concentration and C/D ratio in terms of gender

Dose/concentration/raito	Gender	Total	Controlled-	Uncontrolled-	*P*-value
Dose (g)					
	Male	0.55±0.01	0.53±0.01	0.57±0.02	0.23
	Female	0.50±0.01	0.52±0.02	0.48±0.02	0.18
	P-value	0.029	0.48	0.015	
Plasma concentration (μg/ml)					
	Male	78.0±1.5	76.3±1.9	80.7±2.6	0.17
	Female	77.6±2.1	75.9±2.6	80.4±3.6	0.35
	P-value	0.90	0.90	0.95	
C/D ratio [μg/(ml·g)]					
	Male	155.6±3.7	151.1±3.9	162.9±7.3	0.12
	Female	168.1±5.6	160.2±7.0	180.6±9.2	0.09
	P-value	0.056	0.22	0.14	

Dose, plasma concentration and C/D ratio were expressed as Mean ± SE.

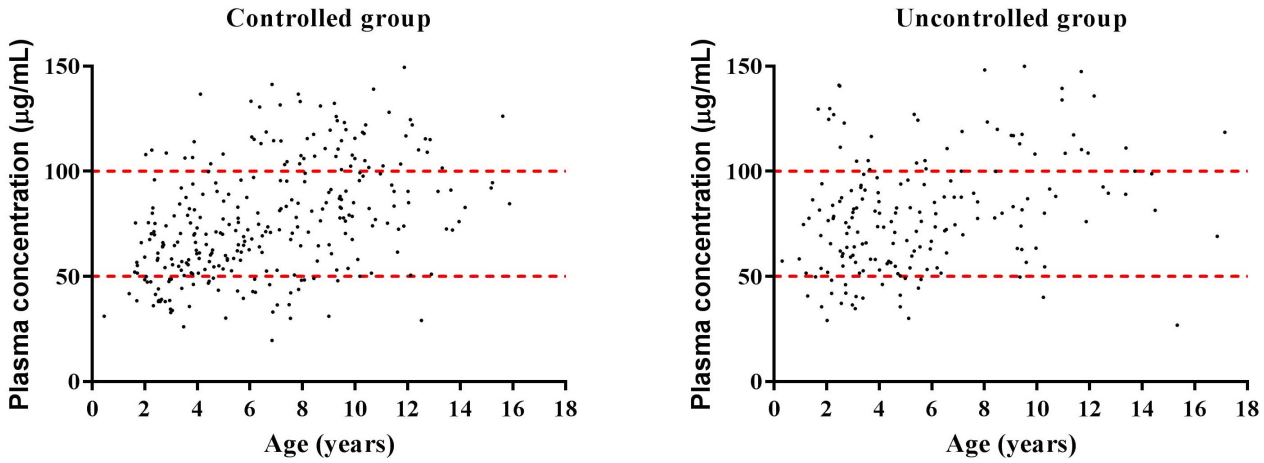

Fig. **1**: The spectrum of trough plasma concentration of VPA. A. Controlled-group B. Uncontrolled-group.

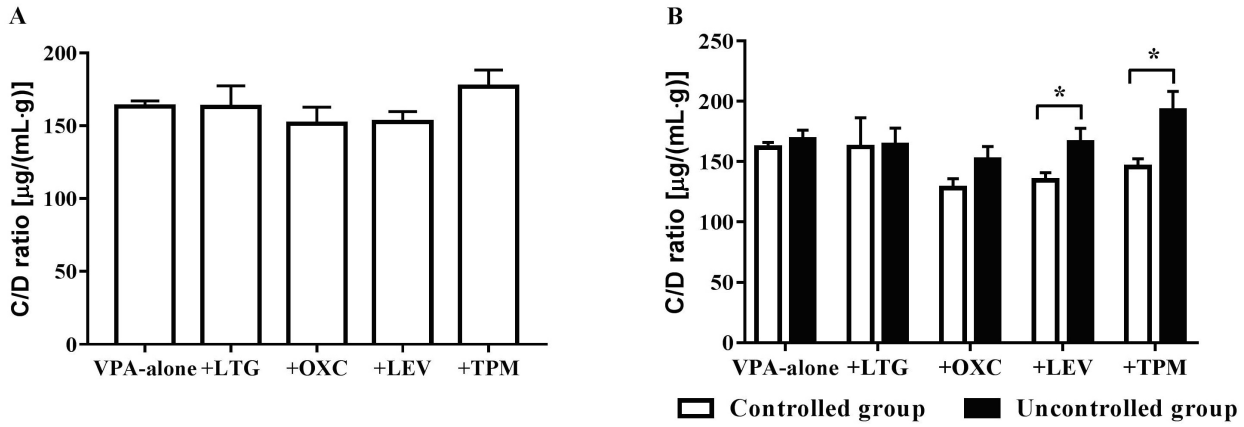

Fig. 2: The impact of co-medication on C/D ratio of VPA. A. In total C/D ratio B. Differences between controlled- and uncontrolled-groups. C/D ratio was expressed as Mean ± SE. Students' T test was applied to each group. * was showed as and $P<0.05$.

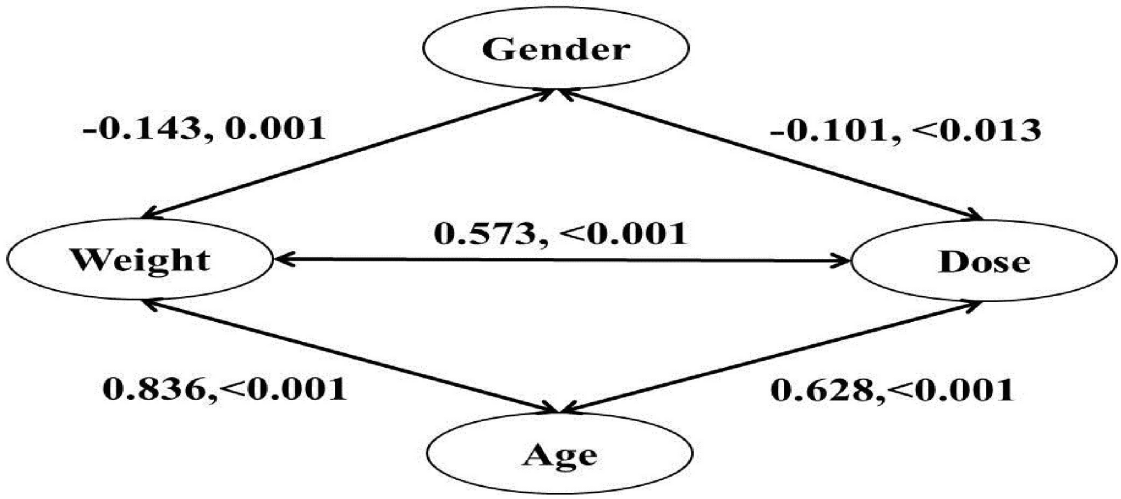

Fig. **3**: Correlation of age, gender, weight and dose. Values were analyzed by stepwise logistic regression through SPSS 19.0 and expressed with r and *P*.

demonstrated that age (12-18years) and comedication could influence the C/D ratio and related to the efficacy of VPA through subgroup analysis.

Several studies had revealed that the VPA concentration did not increase in proportion to VPA dose (Klotz, 2007; Ben *et al*., 2017). Besides, results of our data analyzed by stepwise logistic regression showed that doses were correlated with age, gender and weight (fig. 3). Considering that doses were ascertained by weight in children and to eliminate the multicollinearity of weight and dose, the C/D ratio was used in this study. It suggested that a very low C/D ratio indicated an individual with very fast metabolism, while a very high C/D ratio indicated one with very slow metabolism.

The effect of gender on the VPA concentration was still controversy. FDA advised that it was not necessary to adjust the concentration according to gender. Meanwhile, previous study demonstrated that there was no difference in the ability of combination between adult male and female. However, a recent study found that VPA concentration of female was higher than that of male (Smith *et al*., 2016). In this study, it was confirmed that gender was not associated with the concentration and efficacy of VPA, which agreed to Kodama's study, where it was shown that although the affinity of VPA to serum protein in male patients was approximately 1.4 times higher than in female patients but the total concentration of binding site was 1.2 times greater in female than in male patients (Kodama *et al*., 1999).

Dose was increased with aging and the concentration was elevated. After adjusted by dose or dose per weight, the concentration of infant was lower or higher, which agreed to Chatzistefanidis *et al* research. The low metabolic rate of the infant might account for the tardiness of metabolic for VPA, which was shown in Reith's study that the rate of VPA-glucuronide was significantly decreased in 4-year to 10-year children compared with 11-15 years adolescent. Though it was found that there was no difference on VPA concentration between responsive and resistant groups in 12-18 years children, the latter showed higher C/D which suggested slow metabolism of 12-18 children for VPA might indicate the risk of resistance for VPA. Regarding 2-5 year children, the VPA concentration was higher in the resistant group compared to the responsive group, however, the discrepancy of less than 10μg /mL did not reflect clinical efficacy. Moreover, after adjusting, it was shown that no difference was found.

Many studies had demonstrated that many old AEDs such as carbamazepine, phenytoin, and phenobarbital were proved to accelerate the metabolism of VPA and shorten its half-life, which led to low plasma concentration and inefficiency (Chen *et al*., 2014; May and Rambeck, 1985). Our results showed four new AEDs including LTG, OXC, LEV, and TPM did not influence the C/D ratio of VPA, which agreed with many researches (Otoul *et al*., 2007; Dahlin *et al*., 2010; Coupez *et al*., 2003). However, the C/D ratios of VPA in the uncontrolled group were significantly higher than those in controlled children when combined with LEV and TPM, which was in accordance with the results of Panomvana's study and illustrated that the efficacy of VPA was correlated to the response of target when combined with LEV and TPM (Panomvana Na Ayudhya *et al*., 2006).

CONCLUSION

Age could explain some of the inter-individual pharmacokinetic of VPA, however, gender was not related to the concentration or efficacy of VPA which suggested that concentration monitoring was indispensable to children. Low metabolism, especially in the combination of LEV and TPM, was associated with the resistance of VPA, which maybe a new sight to explore the resistance of VPA.

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