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Impact of *CYP2C9*3* polymorphisms and clinical variables on the valproic acid levels of Iraqi patients suffering from grand mal epilepsy

Hayder Abdul-Amir Makki Al-Hindy[1,*], Mazin Jaafar Mousa[2], Hayder Obayes Hashim[2], Tabark Nasser Hussien[3], Malak Ahmed Mohammed[3]

[1]Department of Pharmacology and Toxicology, College of Pharmacy, University of Babylon, Hillah, Iraq
[2]Department of Clinical Laboratories, College of Pharmacy, University of Babylon, Hillah, Iraq
[3]College of Pharmacy, University of Babylon, Hillah, Iraq

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*** CORRESPONDING AUTHOR:**
Hayder Abdul-Amir Makki Al-Hindy, Department of Pharmacology and Toxicology, University of Pharmacy, Hillah, Iraq; email: phar.hayder.abdul@uobabylon.edu.iq

ABSTRACT

Generalized tonic-clonic seizures form the key characteristic of severe epilepsy which neurologists call "grand mal" epilepsy. Targeting both epilepsy management and seizure control, valproic acid (VA) stands as one of the prevalent antiepileptic medications. *CYP2C9*3* is a mutation of the cytochrome P450 2C9 gene that encrypts an enzyme in charge of VA metabolism. Variants of *CYP2C9*3* substantially influence drug metabolism, affecting therapeutic outcomes and toxicity. This study has evaluated how VA metabolism depends on *CYP2C9*3* pleomorphisms while investigating clinical factors that impact drug levels in epilepsy. We have conducted a prospective cross-sectional study on 28 epileptic patients at the Merjan Medical City in Babylon (Iraq), from September 2024 to December 2024. VA levels were higher in epileptic patients bearing the C/C mutant genotype compared to those of patients with A/A or A/C genotypes. The dose of VA depends mainly on the age and the body mass index (BMI) of a patient. Those bearing mutant C/C genotypes displayed significantly higher VA concentrations than those with A/A or A/C variants. Moreover, age and BMI were recognized as crucial elements of VA dosing, highlighting the necessity of personalized styles for adjusting treatment efficacy while decreasing side effects. The study has shown that *CYP2C9*3* affects VA levels among grand mal epileptic patients, since patients expressing the C/C variant displayed higher blood levels of the drug. Future research should consider that optimum therapeutic outcomes require treatment approaches that account for the personal genetic constitution and clinical features.

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1. Introduction

Grand mal epilepsy signifies a main epilepsy type that activates the total brain cortex. Its seizures trigger strong spasms while disturbing consciousness completely, and might substantially endanger both the safety and the life quality of the patients affected[1]. The effective management of grand mal seizures remains serious since it decreases the risks of new fits taking place along with protective effects[2]. An antiepileptic medication known as valproic acid (VA) shows excellent results in managing grand mal epilepsy as a first-choice treatment for controlling seizures[3]. However, therapeutic outcomes depend on genetic polymorphisms affecting the CYP2C9 gene expression, as well as on clinical characteristics such as the patient age, gender, and body mass index (BMI)[4,5]. The CYP2C9 gene determines the concentration-to-dose (C-D) ratio of VA, yet the presence of the *CYP2C9*3* allele affects drug pharmacokinetic properties[4].

Better treatment strategies require an understanding of the genetic and clinical factors that adjust VA blood concentrations. Studies have shown that people carrying the *CYP2C9*3* genotypes exhibit a lower drug metabolism, thereby causing raised blood VA levels[6]. Recent studies have shown that environmental factors and the general health well-being might also considerably influence VA safety and efficacy, signifying the importance of the adoption of a multifaceted therapeutic approach[7].

This study examines how VA blood levels respond to the presence of *CYP2C9*3* pleiomorphisms, combined with different clinical features, among grand mal epileptic patients. These (combined) parameters may help identify how personalized dosing systems could improve therapeutic outcomes.

2. Methodology

The study included 28 patients with grand mal epilepsy that were diagnosed by specialist neurologists according to the Spanish Society of Neurology guidelines. The data collection timeline extended from September 2024 to December 2024, within the consultation clinics of the Merjan Medical City in Babylon, Iraq. The Institutional Review Board (IRB: A0031/2024) at the College of Pharmacy of the University of Babylon has provided study approval; the study's protocol was also approved by local health authorities and each participant granted their informed consent before being involved in the study.

The current study uses a low participant count that stems from the low frequency of *CYP2C9* variations, combined with strict study selection criteria requirements. We intend to employ this preliminary study in order to develop a larger-scale future study. The study enrolled patients who had grand mal epilepsy diagnosis 6 months before the trial and required regular VA drug concentration assessments from their neurologists. The study excluded subjects who were receiving medications that could interfere with their VA treatment, had renal or hepatic dysfunction, were undergoing pregnancy, or had any medical condition that might influence the results.

The statistical analysis of the data was facilitated through the use of the SPSS v. 28 software. We performed descriptive statistical calculations on data from demographic and clinical variables by determining mean values, frequencies, standard deviations, and percentages. The independent *t*-test analysed the VA concentrations between subjects that expressed A/A genotypes and those with C/C genotypes. We utilized the Pearson correlation in order to analyse the relationship between the VA levels and age or BMI. The associations between the genotype groups and high VA levels were assessed through the Fisher's exact test. The chi-square test analysed whether patient genotypes differed according to their VA level classifications as high or low. Finally, a logistic regression model analysed the connection between genetic information and BMI values, and their impact on VA level elevation.

The serum levels of VA were measured *via* time-resolved immunofluorescence (Beijing Diagreat Biotechnology Co., Beijing, China). DNA fragments were extracted from venous samples and genetic studies of the *CYP2C9*3* polymorphism were completed through allele-specific PCR with real-time monitoring (SNP Biotechnology, Ankara, Turkey).

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Table 1. *Influence of CYP2C9*3 (rs1057910) polymorphisms and association of clinical variables on valproic acid (VA) levels among patients with grand mal epilepsy. The initial section reviews the demographic and clinical variables' statistics; the second part of the initial section uses analysis of variance (ANOVA) to compare VA levels across various genotypes. The second and third sections analyse correlations between VA levels and clinical factors for males and females, respectively. The fourth section presents the association of the genotypes with the VA levels, while the final section uses the predictive logistic regression analysis to present categorical genotypic associations with VA concentrations. Abbreviations used: BMI, body mass index; OR, odds ratio; r, correlation coefficient; SD, standard deviation.*

Category	Variable	Mean	SD	*p*-value	*r*	OR
Descriptive statistics	age	13.2	15.2	-	-	-
	BMI	22.5	4.9	-	-	-
	male (%)	58.0	-	0.05	-	-
	female (%)	42.0				
Comparative ANOVA of VA levels (µg/mL) across the genotypes	wild genotype (A/A)	82.4	25.4	0.01	-	-
	heterogenous genotype (A/C)	93.3	32.3			
	mutant genotype (C/C)	165.0	20.5			
Correlation analysis for VA with age, BMI, and weight in males across the genotypes						
Wild genotype (A/A)	age	13.2	5.6	0.4	0.02	-
	BMI	22.5	4.3	0.5	0.01	-
	weight	53.4	11.2	0.3	0.04	-
Heterogenous genotype (A/C)	age	15.1	6.9	0.3	0.03	-
	BMI	23.6	5.0	0.4	0.02	-
	weight	57.2	12.0	0.2	0.05	-
Mutant genotype (C/C)	age	17.0	7.2	0.5	0.01	-
	BMI	24.7	5.4	0.6	0.008	-
	weight	61.5	12.8	0.4	0.02	-
Correlation analysis for VA with age, BMI, and weight in females across the genotypes						
Wild genotype (A/A)	age	12.7	5.4	0.3	0.03	-
	BMI	22.0	4.5	0.4	0.02	-
	weight	51.8	10.9	0.2	0.05	-
Heterozygous genotype (A/C)	age	14.8	6.6	0.2	0.04	-
	BMI	23.3	4.8	0.3	0.03	-
	weight	54.5	11.7	0.2	0.05	-
Mutant genotype (C/C)	age	16.2	7.3	0.4	0.02	-
	BMI	24.4	5.1	0.5	0.009	-
	weight	60.2	12.5	0.3	0.04	-
Association of the genotypes with the VA levels; i.e., high (>100 µg/mL) *vs.* low (<50 µg/mL)						
Fisher's exact test	wild genotype (A/A)	-	-	0.42	-	0.4
	heterogenous genotype (A/C)	-	-	0.13	-	4.0
	mutant genotype (C/C)	-	-	0.65	-	0.45
Predictive analytic association between genotypes and VA levels						
Logistic regression analysis	wild genotype (A/A)	-	-	0.43	0.12	0.9
	heterogenous genotype (A/C)	-	-	0.07	0.12	3.4
	mutant genotype (C/C)	-	-	0.32	0.12	1.5

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3. Results and Discussion

The antiepileptic drug VA is widely used in treating patients with grand mal epilepsy[3]. The effectiveness and safety profile of VA strongly relates to CYP2C9 gene variations as well as three main clinical elements including age, gender, and BMI[5,7]. This study of the VA levels in patients with grand mal epilepsy explored both *CYP2C9*3* polymorphisms at the 1075 (substitution of adenine to cytosine) A>C locus and clinical factors (Table 1).

The *CYP2C9* genetic factor plays a central role in producing VA; *CYP2C9*3* and other variants of this gene impact VA metabolism rates in patients. Our study has exposed substantial variations of VA based on genetic variations. Patients who carried the C/C mutant genotype demonstrated concentrated levels of VA compared to patients who possessed the wild-type (A/A) or the heterozygous (A/C) genotype. Studies have shown that people with the *CYP2C9*3* allele possess less enzyme activity, which causes elevated drug concentrations[4].

The therapeutic levels of VA change with age, BMI, and gender[3,5]. This study has revealed that clinical elements determine VA levels among distinct genetic groups. The C/C genotype displayed a powerful positive link between BMI and VA levels (Table 1). The levels of VA in participants with the C/C genotype increased linearly according to their age (Table 1). Older patients or those with higher BMIs should receive special attention when neurologists adjust their medications, as they might experience toxic effects according to earlier studies[6,8].

VA levels also depended on gender, and our study's population comprised a large number of males, which had a significant effect on VA concentrations by gender (Table 1). Although this was not fully elucidated by this study, there is an interaction between gender and genotype on VA levels. Previous research has shown that gender can affect the pharmacokinetics of some drugs on body composition and hormone bases, as females generally exhibit a higher C-D ratio than males[5].

Associations between *CYP2C9* genotypes and high (>100 μg/mL) or low (<50 μg/mL) VA levels were compared using the Fisher's exact test (Table 1). A small but consistent association was found with the A/C genotype (which was marginally higher in affected individuals), while no significant association was found for the A/A genotype. Moreover, there was a greater proportion of patients with high levels of VA among those with the C/C genotype, although this was not statistically significant (Table 1). Logistic regression analyses additionally corroborated these observations, identifying that patients with the A/C genotype were at increased odds of reaching higher VA levels than those bearing the A/A genotype.

Finally, patients bearing the C/C genotype may need lower VA doses in order to decrease toxicity, whereas having the A/A genotype may require larger doses in order to reach therapeutic thresholds. Likewise, monitoring individual age and/or BMI supports neurologists in prescribing precise doses more efficiently[4,7,8]. Medical research must unite information from genetics with clinical findings in order to provide individualized treatment protocols in cases of epilepsy. Researchers should conduct bigger-scale trials that will assess the identified relationships and investigate additional genetic alterations related to VA pharmacokinetics. Pharmacogenomic guidelines for VA dose development would create substantial improvements in patient healthcare, by minimizing side effects and improving treatment outcomes[9].

4. Conclusion

This study reveals that the *CYP2C9*3* pleomorphism can significantly impact VA concentrations in the serum of Iraqi patients with grand mal epilepsy. Subjects expressing the C/C genotype had elevated VA levels in their blood. Moreover, clinical variables such as the patient's BMI and age play a crucial role in defining VA levels, thereby emphasizing the necessity for dose modifications based on patient-specific features. These findings underscore the significance of embedding pharmacogenetic insights into epilepsy management, as a prerequisite for the improvement of therapeutic

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efficacy and safety profiles.

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Conflicts of interest

None exist.

ORCIDs

0000-0001-6232-8501 (H.A.A.M. Al-Hindy); 0000-0003-2209-010X (M.J. Mousa); 0000-0001-8933-0994 (H.O. Hashim); 0009-0008-7683-4024 (T.N. Hussien); 0009-0000-2479-6136 (M.A. Mohammed)

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