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Research Article

Study of CYP2C9 and CYP2C19 polymorphisms in a Romanian epilepsy population

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Abstract. The CYP2C9 and CYP2C19 enzymes metabolize a wide range of drugs, among which are antiepileptic drugs. Objective: To determine the frequencies of CYP2C9 and CYP2C19 genetic variants in epilepsy and to compare it with a health population. Materials and method: 101 patients with epilepsy, with a mean age of 39.24±13.74, evaluated in the Neurology Clinic of Cluj-Napoca and Neurology Department of Deva County Hospital were included. Using the PCR-RFLP method we have determined allelic variants of CYP2C9 and CYP2C19 polymorphisms for each patient. Results: For the CYP2C9 polymorphisms we fund 63 homozygous for a wild type allele, (62.4%), 19 individuals (18.8%) heterozygous for CYP2C9*2, 15 individuals (14.9%), heterozygous for CYP2C9*3, 2 individuals (2%) homozygous for CYP2C9*2 and 2 individuals (2%) *2/*3 heterozygote. In case of CYP2C19 polymorphisms 74 patients (73.3%) were homozygous for a wild-type allele, 20 individuals (19.8%) were heterozygous for CYP2C19*2 and 7 individuals (14.9%) were homozygous for CYP2C19*2. We did not find any *1/*3, *1/*4, *2/*3, *3/*3, *3/*4, *4/*4 genotypes. The distribution of the CYP2C9 and CYP2C19 alleles in the epilepsy population matches data from reports on other Caucasian healthy populations.

Key Words: epilepsy, genotyping, Romanian population, poor-metabolizer.

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Introduction

Patients diagnosed with epilepsy and receiving antiepileptic drug therapy can have very different responses to treatment, as well as variable risk of side effects. This variability might be partially determined by the polymorphisms of genes coding the drug-metabolizing enzymes.The CYP2C subfamily of cytochrome P450 comprises 4 members: CYP2C8, CYP2C9, CYP2C18 and CYP2C19. The genes encoding these enzymes are polymorphic. CYP2C9 hydroxylates about 15% of drugs in current clinical use. Several variants of the CYP2C9 gene have been described, but the most prevalent and most frequently studied variants are the CYP2C9*2 and CYP2C9*3 polymorphisms (Kim et al. 2004). From a clinical perspective, therapy with low therapeutic index drugs such as antivitamin K, antidiabetic sulfonamides and phenytoin can be influenced by the reduction in CYP2C9 metabolic activity, causing problems in determining the dosage or determining toxic effects (Militaru *et al* 2012a, b). CYP2C19 is important in the biotransformation of some anticonvulsants (S-mephenytoin and diazepam) (Ono et al 1996) but also for other important drugs, such as proton pump inhibitors, clopidogrel and antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors)(Gardiner & Begg 2006). The estimated fraction of responsibility for drug metabolism in phase 1 reactions for CYP2C19 is 5%. Seven variants (*2–*8) in the CYP2C19 gene have been associated with reduced enzyme activity in vivo, largely due to production of inactive enzyme protein (Ingelman-Sundberg *et al* 2005). The most common variants are *2 and *3. However, the CYP2C19*17 variant is associated with an ultrarapid metabolism phenotype (Sim *et al* 2006).

This study is designed to determine the distribution of CYP2C9 and CYP2C19 polymorphisms in a Romanian epileptic population and to make a comparison between the population with epilepsy and a healthy population, regarding the distribution of the major mutant alleles that determine the poor-metabolizer status.

Materials and methods

A number of 101 epilepsy patients, aged between 19 and 76, admitted to the Neurology Hospital Cluj-Napoca and to the Neurology Department of the Deva County Hospital between 2008 and 2010 was included in this study. All participants originated from the Transylvania region (North-Western and central parts of Romania). The study group comprised 58 women (57.4%) and 43 men (42.6%). The patients were assessed according to international diagnostic criteria to establish the type of epilepsy (idiopathic or secondary) (Berg *et al* 2010). The study was approved by the Iuliu Hatieganu University of Medicine and Pharmacy Ethic Committee and each patient was informed and signed an Informed Consent.

Genotyping

After admission to the study, 3 mL of peripheral blood were drawn on EDTA. DNA was extracted from peripheral blood leukocytes using a commercially available kit (Wizard Genomic DNA Purification Kit, Promega, Madison, USA). The CYP2C19*2, *3 and *4 alleles were studied using the PCR-RFLP technique, according to partially modified, previously described protocols (DeMorais *et al* 1996 a, b; Ferguson *et al* 1998).The PCR reactions were carried out in an Eppendorf thermocycler (Mastercycler Gradient, Eppendorf, Germany). The amplification products were digested with SmaI restriction enzyme (5U at 30°C) for CYP2C19*2, BamHI (10Uat 37°C) for CYP2C19*3 and PstI (5U at 37°C) for CYP2C19*3 (Fermentas MBI, Vilnius, Lithuania). The digested PCR products were resolved by electrophoresis in 2.5% agarose gels stained with ethidium bromide. Genotyping for the CYP2C9*2 and CYP2C9*3 polymorphisms was performed with PCR-RFLP as previously described by Aynacioglu (Aynacioglu 1998). A 372-bp amplicon was digested overnight with the Sau96I restriction enzyme (Fermentas MBI, Vilnius, Lithuania), giving rise to 3 fragments with lengths of 179, 119 and 74 bp in the case of the wild-type allele and to only 2 fragments, with lengths of 253 and 119 bp for CYP2C9*2 allele. To analyze the CYP2C9*3 variant, a 130-bp fragment was obtained by PCR and digested overnight with the StyI restriction enzyme (Fermentas MBI). The wild-type allele was resistant to the StyI digestion and the CYP2C9*3 allele creates a restriction site for StyI obtaining 2 fragments, with lengths of 104 and 26 bp.

Statistical analysis

The observed genotype and allele frequencies were compared to the expected frequencies, in order to verify the Hardy-Weinberg equilibrium. Allele and genotype frequencies were compared between the epileptic population and other populations using the chi-square test. We also compared allele and genotype frequencies between idiopathic and secondary epilepsy. The statistical analysis was performed using the software SPSS 17th version, considering a value of $p<0.05$ statistically significant.

Results

Characteristics of epileptic patients are presented in Table 1. There are no differences between male and female patients regarding the age or the type of epilepsy.

Table 1. Characteristics of epileptic patients

		Male N=43	Female N=58	Total	
Age		39.53 ±13.11	39.02 ±14.3	39.24 ±13.74	p= 0.347
Epilepsy	Idiopathic	28 (65.1%)	33 (56.9%)	61 (60.4%)	p=0.404
	Secondary	15 (34.9%)	25 (43.1%)	40 (39.6%)	

Studies previously conducted in the same geographical area (Buzoianu *et al* 2010, 2012) were used as controls. For the CYP2C9 polymorphisms, the majority of individuals were homozygous for a wild type allele, 63 (62.4%). Nineteen individuals (18.8%) were heterozygous for CYP2C9*2, whereas 15 individuals (14.9%) were heterozygous for CYP2C9*3. Two individuals (2%) were homozygous for CYP2C9*2, whereas 2 individuals (2%) were CYP2C9*2/CYP2C9*3 compound heterozygote. Thus, 4 individuals (3.9%) from the analyzed cohort are predicted to have the lowest CYP2C9 enzymatic activity, with respect to the CYP2C9*2 and CYP2C9*3. Overall, the CYP2C9*2 allele had a frequency of 12.3%, whereas the CYP2C9*3 allele had a frequency of 8.4%. The genotype *3/*3 was not observed in the studied population. The observed genotype frequencies for CYP2C9 polymorphisms were consistent with the Hardy–Weinberg equilibrium (p=0.39).The results regarding the distribution of CYP2C9*2 and CYP2C9*3 are shown in detail in Table 2 and 3. The absence of the CYP2C9*2 or CYP2C9*3 polymorphisms was considered as a wild-type allele. In comparison with the non-epileptic patients selected from the same geographical area (Buzoianu *et al* 2012), no statistically significant differences were observed between the epileptic and non-epileptic populations as regards genotype frequencies (Table 2) and allele frequencies (Table 3).

Table 2. Genotype frequencies observed for the CYP2C9 polymorphisms in our study

CYP2C9 genotypes	Epilepsy n (%)	Control n (%) Buzoianu et al 2012	p
***1/*1**	63 (62.4)	209 (63)	0.746
***1/*2**	19 (18.8)	62 (18.7)	
***2/*2**	2 (2)	2 (0.6)	
***1/*3**	15 (14.9)	47 (14.1)	
***2/*3**	2 (2)	9 (2.7)	
***3/*3**	0	3 (0.9)	

Table 3. Allele frequencies observed for the CYP2C9 polymorphisms in our study, compared to non epileptics

CYP2C9 Alleles	Epilepsy n=202 (%)	Control n=664 (%) Buzoianu et al 2012	p
***1**	160 (79.2)	527 (79.3)	0.86
***2**	25 (12.37)	75 (11.3)	
***3**	17 (8.4)	62 (9.4)	

Although genotypes *2/*2 and *2/*3 were not observed in patients with idiopathic epilepsy, there are no statistically significant differences between the two epileptic groups as concerns genotype frequencies (p= 0.154) and allele frequencies (p=0.409) (Table 4 and 5).

In case of CYP2C19 polymorphisms, most of the patients were homozygous for a wild-type allele, 74 (73.3%). Twenty individuals (19.8%) were heterozygous for CYP2C19*2, whereas 7 individuals (14.9%) were homozygous for CYP2C19*2, thus

are predicted to have the lowest CYP2C19 enzymatic activity. We did not find any *1/*3, *1/*4, *2/*3, *3/*3, *3/*4, *4/*4 genotypes in our study of population of epileptics. The observed genotype frequencies for CYP2C9 polymorphisms were deviated from Hardy–Weinberg equilibrium (p=0.0032). The absence of the CYP2C19*2, CYP2C19*3 or CYP2C19*4 polymorphisms was considered as a wild-type allele.

Table 4. Compared frequencies of CYP2C9 genotypes between idiopathic and secondary epilepsy groups.

CYP2C9 genotypes	Idiopathic epilepsy n (%)	Secondary epilepsy n (%)	p
***1/*1**	39 (63.9%)	24 (60%)	
***1/*2**	13 (21.3%)	6 (15%)	
*2/*2	0	2 (5%)	0.154
***1/*3**	9 (14.8%)	6 (15%)	
*2/*3	0	2 (5%)	

Table 5. Compared frequencies of CYP2C9 alleles between idiopathic and secondary epilepsy groups.

CYP2C9 alleles	Idiopathic epilepsy n (%) 122	Secondary epilepsy n (%) 80	p
***1**	100 (82%)	60 (75%)	
***2**	13 (10.7%)	10 (12.5%)	0.409
***3**	9 (7.3%)	10 (12.5%)	

In case of CYP2C19 polymorphisms, most of the patients were homozygous for a wild-type allele, 74 (73.3%). Twenty individuals (19.8%) were heterozygous for CYP2C19*2, whereas 7 individuals (14.9%) were homozygous for CYP2C19*2, thus are predicted to have the lowest CYP2C19 enzymatic activity. We did not find any *1/*3, *1/*4, *2/*3, *3/*3, *3/*4, *4/*4 genotypes in our study of population of epileptics. The observed genotype frequencies for CYP2C9 polymorphisms were deviated from Hardy–Weinberg equilibrium (p=0.0032). The absence of the CYP2C19*2, CYP2C19*3 or CYP2C19*4 polymorphisms was considered as a wild-type allele.

Frequencies were compared to the control group in the same geographical area (Buzoianu *et al* 2010) and no statistically significant differences were observed between genotype frequencies CYP2C9 (Table 6) and allele frequencies (Table 7). Also, no significant differences were observed between genotype or allele frequencies in the two groups of (idiopathic or secondary) epilepsy patients (Tables 8, 9).

Discussions

Recent evolutions in pharmacogenetics have determined the evaluation of antiepileptic drug tolerance and efficiency and even caused changes in treatment guidelines, such as the recommendation to perform screening for HLA-B*1502 allele in Asian populations, before beginning treatment with carbamazepine, due to a much higher frequency of severe skin reactions in these populations (Chung *et al* 2010). Poor metabolizer phenotype can alter the clearance of certain antiepileptic drugs, as demonstrated by Goto *et al* in the case of phenytoin (Goto *et al* 2007).

Table 6. Genotype frequencies observed for the CYP2C19 polymorphisms in our study

CYP2C19 genotypes	Epilepsy n=101 (%)	Control n=200 (%) Buzoianu et al 2010	p
***1/*1**	74 (73.3)	148 (74)	
***1/*2**	20 (19.8)	48 (24)	0.072
***2/*2**	7 (6.9)	3 (1.5)	
***2/*4**	0	1 (0.5)	

Table 7. Allele frequencies observed for the CYP2C19 polymorphisms in our study

CYP2C19 Alleles	Epilepsy n=202 (%)	Control n=400 (%) Buzoianu et al 2010	p
***1**	168 (83,2)	344 (86)	
***2**	34 (16,8)	55 (13.75)	0.474
***4**	0	1 (0.25)	

Table 8. Compared frequencies of CYP2C9 genotypes between idiopathic and secondary epilepsy groups.

CYP2C19 genotypes	Idiopathic epilepsy n=61	Secondary epilepsy n=40	p
***1/*1**	42 (68.9%)	32(80%)	
***1/*2**	14 (23%)	6 (15%)	0.464
***2/*2**	5 (8.1%)	2 (5%)	

Table 9. Compared frequencies of CYP2C9 alleles between idiopathic and secondary epilepsy groups.

CYP2C19 Alleles	Idiopathic epilepsy n=122(%)	Secondary epilepsy n=80	p
***1**	98 (80.3%)	70 (87.5%)	0.248
***2**	24 (19.7%)	10 (12.5%)	

Allele and genotype frequency in the studied epileptic population does not differ from the frequency in the general population. CYP2C9*2 and CYP2C9*3, as demonstrated by our study and other studies conducted on Romanian population, have a much higher frequency in Romanians than in Asian (Kimura *et al* 1998; Yang *et al* 2003) or African populations (Hamdy *et al* 2002; Allabi *et al* 2003), where these variants are very rare or sometimes absent. The CYP2C19*3 allele, which was absent in our population group, is specific to Asian (Lamba *et al* 2000) and Pacific ethnical groups (Griese 2001).The frequencies for both CYP2C9 and CYP2C19 are similar to those observed in most of the Caucasian populations living in Europe (Scordo *et al* 2004; Sipeky *et al* 2009). For CYP2C19 mutations, even though a deviation from the Hardy-Weiberg equilibrium of genotype frequencies is observed in epileptic patients,

such difference is not observed for allele frequencies and there are no statistically significant differences between the epileptic group and the control group. This error is probably due to the small number of patients in the study.

Phenytoin, a commonly used antiepileptic drug, is an example of medication determining interindividual pharmacokinetic differences, largely due to genetic factors, such as CYP2C9 polymorphism. Phenytoin is frequently used as an antiepileptic, in spite of its non-linear, complex pharmacokinetics and its low therapeutic index. Given also the toxicity to the central nervous system, genotyping may be useful. Phenytoin is metabolized mostly by CYP2C9 enzyme and partially by CYP2C19 enzyme. Both CYP2C9 *2 and *3 alleles lead to a significant reduction in the enzymatic activity of the CYP2C9 that determine a substantial increase in phenytoin AUCs. The highest values (4- to 5-fold) are found in those with CYP2C9 genotypes associated with very low enzyme activity (e.g.,CYP2C9*3/*3) (Kidd *et al* 1999, 2001) thus requiring an evaluation of dosage regimens for phenytoin in certain patients based on their genetic status (Taguchi *et al* 2005). Attempts have been made to establish both phenytoin and carbamazepine protocols to determine maximum allowed doses, based on genetic variants, to prevent the risk of toxicity (Tate *et al* 2005). Due to the low therapeutic index of phenytoin, Klotz (Klotz 2007) suggests reducing the dose in patients with mutant alleles, both for CYP2C9 and CYP2C19. Jiang et al (2009) showed that the presence of mutant alleles for CYP2C9 and CYP2C19 significantly influences the pharmacokinetic variability of valproic acid in Chinese epileptic patients. The metabolism of valproate, commonly used in treating epilepsy, has been found to be influenced by the CYP2C9 polymorphism (Ingelman-Sundberg 2004), but the evidence is inconclusive and currently there are no recommendations for modifying the dosage based on genetic variants.

As regards the association of mutant alleles for CYP2C9 and CYP2C19, our study observed only two cases of CYP2C9 *1/ *2 associated with CYP2C19 *1/*2 and two cases of CYP2C9 *1/*3 associated with CYP2C19 *1/*2. No CYP2C9 and CYP2C19 associations of mutant alleles, the homozygote form, were observed in our study. If we only take into account the presence of mutant alleles for both CYP2C9 and CYP2C19, we can estimate that 3.8% of the epileptic patients will require adjustments to the antiepileptic drug treatment, due to the presence of mutations determining the poor metabolizer status.

Conclusion

Genetic variant alterations may affect the efficacy, tolerability, and safety of antiepileptic drugs. It is essential to determine the practical relevance of genotyping, given that is currently an expensive solution when compared to other treatment monitoring methods.

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