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Research Article

# The influence of CYP2C9, CYP2C19 and ABCB1 polymorphisms on the plasma concentrations of valproic acid in epileptic patients

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**Abstract.** The aim of the study was to evaluate the variations between plasma concentrations of valproic acid, an antiepileptic drug, based on gene polymorphisms in microsomal enzymes CYP2C9, CYP2C19 and the transporter protein P-gp (ABCB1) to make a correlation between plasma concentrations and certain genetic mutations. Materials and method: 74 patients with epilepsy, evaluated in the Neurology Clinic of Cluj-Napoca were included. All patients were under stable VPA treatment for at least a month. Steady state plasma concentrations were determined using the GC/FID technique. Using the PCR-RFLP method we have determined ABCB1 C3435T, G2677T/A, T129C , CYP2C9, CYP2C19 polymorphisms . Results The mean VPA plasmatic level was 70.55±29.78 mg·L-1. Most of the patients (62.16%) had therapeutic levels of VPA, between 50 and 100 mg·L-1. The observed polymorphisms for ABCB1 C3435T, G2677T, and CYP2C19 do not significantly influence the VPA plasmatic concentrations or the dose-adjusted-VPA-concentrations compared to wild genotype. The CYP2C9 *2/*3 genotype increases VPA concentrations to higher than therapeutic values (110.12±44.99 mg·L-1). The presence of allele C for 129 determines a statistically significant decrease in VPA plasmatic concentrations to lower than therapeutic values (40.78±29.01 mg·L-1) Conclusions. In our study we found no significant differences between different genetic groups in VPA concentration, except for ABCB1 T129C TC genotype, who reduced VPA concentrations.

**Key Words:** valproic acid, epilepsy, CYP2C9, CYP2C19, MDR1 (ABCB1) gene.



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## Introduction

The epilepsy is a major health problem and one third of patients are having a resistant to antiepileptic medication form of disease. For these patients, epilepsy is indeed a disabling disease; it is associated with increased morbidity and mortality and with serious social and emotional consequences (Berg et al 2010). There are many possible causes involved in uncontrolled epilepsy. The resistance is a multifactorial phenomenon, depending on genetic factors, disease-related factors (the etiology of the seizures, progression of epilepsy under correct treatment), alterations in drug targets or alterations in drug uptake into the brain. These are some of the possible factors involved in this type of disease. A full evaluation of all the factors used for establishing a risk for resistant epilepsy is very useful for making early predictions and to determine faster interventions (eg surgical therapy) (Kwan et al 2010; Kwan et al 2000)

Valproic acid (VPA) is one of the most prescribed anti-epileptic drugs (AEDs). Interindividual variability of the doses used and serum levels may reflect functional consequences of genetic mutations in genes encoding metabolic enzymes (Tan et al 2010). VPA metabolism is performed first three types of reactions, glucuronide conjugation, mitochondrial beta-oxidation and hydroxylation by CYP P450 catabolism, especially CYP2C9. It is estimated that between 20 and 70% of valproate is eliminated in urine as glucuronide conjugate (Guo et al 2012; Kiang et al 2006). Genetic mutations in the MDR1 gene encoding the efflux protein P-gp may influence the pharmacokinetics of AEDs, both on the intestinal absorption and the distribution of the drug. In fact one of the emerging multi-resistant to antiepileptic drugs theories considering its efflux protein function at the blood-brain barrier (Schinkel et al 1996, Sills et al 2002). The overexpression of multidrug transporters in patients with pharmaco-resistant epilepsy is not restricted to the brain. This occurs also in other tissues, such as the small intestine. (Berggren et al 2007). Here the P-gp forms a barrier against entrance of some substances, including drugs, from the intestinal lumen into the blood, limiting their oral bioavailability. (Giacomini et al 2010) This study examines the variations of plasma concentrations of VPA based on gene polymorphisms in microsomal enzymes CYP2C9, CYP2C19 and the transporter protein P-gp (ABCB1) to make a correlation between plasma concentrations and certain genetic mutations. Secondarily, the correlation between other clinical factors (eg. treatment response) and the plasma concentrations of valproic acid is determined.

## Material and method

The study evaluated 74 epileptic patients admitted in Neurology Hospital Cluj-Napoca, receiving therapy with VPA (as an unique

Table 1 Genetic study

| Gene | Allele | SNP | Primers | PCR protocol |
|---|---|---|---|---|
| MDR1 (ABCB1) | C3435T - C/T | rs1045642 | Fw 5'-TTG ATG GCAAAG AAA TAA AGC-3'<br>Rev 5'- CTTACA TTA GGC AGT GAC TCG –3' | modified PCR-RFLP protocol *Li et al 2006 |
| | T129C - T/C | rs3213619 | Fwd: 5'-TCAGCA TTC AGT CAA TCC GG-3'<br>Rev: 5'-TTT GCG TGC CCC TAC CTC-3'. | PCR-RFLP Moriya et al 2002 |
| | G2677A/T-G/T/A | rs2032582 | Fw 5'-TTT GCAGGC TAT AGG TTC CAG-3';<br>Rev G2677A, 5'-GTT TGA CTC ACC TTC CCA G-3';<br>Rev G2677T 5'-TTT AGT TTG ACT CAC CTT CCC G-3' | PCR-RFLP Moriya et al 2002 |
| CYP2C9 | 2* 430C/T | rs1799853 | Fw5'TACAAATACAATGAAAATATCA3'<br>Rev 5' TAACAACCAGACTCATAATG 3' | PCR-RFLP van Oijen et al 2005 |
| | 3* 1075A/C | rs1057910 | Fw 5' TGCACGAGGTCCAGAGGTAC-3'<br>Rev 5' GATACTATGAATTTGGGACTTC-3' | PCR-RFLP van Oijen et al 2005 |
| CYP2C19 | 2* splice site defect | rs4244285 | Fw 5'-AATTACAACCAGAGCTTGGC-3'<br>Rev 5'-TATCACTTTCCATAAAAGCAAG-3' | PCR-RFLP Zand et al 2007 |
| | 3* premature stop codon | rs4986893 | Fw 5'-TATTATTATCTGTTAACTAATATGA-3'<br>Rev 5' -ACTTCAGGGCTTGGTCAATA-3' | PCR-RFLP Zand et al 2007 |

antiepileptic drug or associated with other antiepileptic drugs ), patients in steady state (constant dose for approximately one month). Patients were followed for one year, at least four visits, to determine whether or not patients respond to treatment. Patients were instructed to use a self-assessment seizures diary to note their current medication, doses and any omissions in doses. They were assessed according to international diagnostic criteria to establish the type of epilepsy (idiopathic or secondary) and the type of response to antiepileptic therapy (responder if there were no crises in one year of follow-up or non-responder) (Kwan et al 2010). We excluded from the study patients with undefined therapeutic responses (according to the ILAE criteria), ie the patients with a response to an appropriate therapy that cannot be defined either as responder nor non-responder,( ie patients who had stopped having seizures, but not yet satisfied the criterion of time or patients who have seizures, but attempted only one regimen)

All patients were tested for serum concentrations of VPA and genetic polymorphisms of CYP2C9, CYP2C19 and ABCB1. A dose-adjusted concentration of VPA was also calculated as the trough concentration divided by the corresponding dose of VPA (mg/m$^2$/day).

The study was approved by University of Medicine and Pharmacy Ethic Committee and an Informed Consent was signed.

**Blood Sampling and VPA Assays**

The blood samples (5 ml) were obtained using an EDTA tube and centrifuged (5000 rpm for 10 min) in the first 4 hours, followed by plasma separation and freezing at -20$^0$C until the determination of concentrations. A simple capillary gas chromatographic assay with liquid-liquid extraction and flame ionization detection (GC/FID) was used for the determination of VPA in human plasma. Determinations were performed using an Agilent 6890N GC system. The analytical range for VPA was between 5.215 and 333.76 mg·l$^{-1}$. The method had excellent linear correlation (r=0.999). The limit of detection was 0.34 mg·l$^{-1}$ (Buzoianu et al 2011).

**Genetic analysis**

Genotyping was conducted using DNA extracted from lymphocytes of peripheral blood. DNA extraction
was effected using commercial kits for genomic DNA extraction (Wizzard Genomic DNA Purification Kit, Promega, USA) We selected seven SNPs including ABCB1 rs1045642, rs3213619, rs2032582, CYP2C9 rs1799853, rs1057910 and CYP2C19 rs4244285, rs4986893 for this study We used different PCR-RFLP protocols to determine the established polymorphisms (table 1). The primers sequences used for amplification are marked in table 1. We analysed fragments resulted after digestion in a 2% agarose gel. Gels were coloured with ethidium bromide, and visualized using a photo-documentation and gel analysis system (Vilber Lourmat Imaging System®).

The distribution of genotypes for each polymorphism was assessed for deviation from Hardy-Weinberg equilibrium (HWE), and differences in genotype frequency and in allele frequency between the groups were assessed using the $\chi 2$ test. Characteristics of the study groups were expressed as mean and standard deviation (for normal distribution, using Kolmogorov-Smirnov test) or median and interquartile range or number (for abnormal distribution). Student's t test was used for normally distributed data and the Mann Whitney U test was used for data that were abnormally distributed to compare pharmacokinetic data (VPA doses, VPA serum concentrations and dose-adjusted-VPA concentration) and the response to treatment. The comparison between groups of patients based on the CYP 2C9, CYP2C19 and ABCB1 genotypes was examined using the t test or a one-way ANOVA . All analyses were performed with SPSS statistical analysis software, version 18.0 (SPSS, Chicago, IL, USA). A statistically significant difference was considered at $p<0.05$.

Table 2 Summary data for epileptic patients (no/ mean±SD/ median)

| Variables | Treatment | | | Type of epilepsy | | |
|---|---|---|---|---|---|---|
| | Monotherapy VPA (n=32) | Polytherapy (n=42) | p | Idiopathic (n=46) | Secondary (n=28) | p |
| **Gender (M/F)** | 17/15 | 14/28 | 0.1 | 19/27 | Dec-16 | 0.54 |
| **Age** | 36.88±14.1 | 41.83±14.4 | 0.14 | 38.93±14.38 | 40.93±14.39 | 0.56 |
| **Body surface** | 1.88±0.22 | 1.799±0.2 | 0.07 | 1.838±0.22 | 1.83±0.19 | 0.98 |
| **VPA dose (mg) - median** | 1000 (700-1000) | 1000 (1000-1500) | 0.05 | 1000 (1000-1125) | 1000 (1000-1500) | 0.87 |
| **Body-surface adjusted VPA dose ($mg/m^2$)** | 484.84±16 | 649.95±200.9 | <0.001 | 582.01±187.74 | 572.88±231.57 | 0.85 |
| **Concentration VPA (mg/l)** | 70.24±29.73 | 70.78±30.17 | 0.93 | 72.05±30.13 | 68.08±29.57 | 0.58 |
| **Dose adjusted VPA concentration** | 158.92±71.58 | 121±75.53 | 0.32 | 138.37±83.15 | 135.81±75.75 | 0.88 |

Table 3. Summary pharmacokinetic date for epileptic patients in function of therapeutic response

| Variables | Response (n=56) | | |
|---|---|---|---|
| | Responder (n=28) | Non-responder (n=28) | p |
| **VPA dose (mg) - median** | 1000 (700-1000) | 1250 (1000-1500) | <0.001 |
| **concentration VPA ( $mg \cdot l^{-1}$)** | 76.16±30.05 | 72.43±28.14 | 0.63 |
| **dose adjusted VPA concentration** | 173.09±90.78 | 104.17±43.84 | 0.001 |

Table 4. Summary of correlations between genetic data and VPA concentrations

| Variables | | Genotype frequency N=74 (%) | VPA concentration (mg/l) | p | Dose-adjusted VPA concentration (mg/dl) | p |
|---|---|---|---|---|---|---|
| **CYP 2C9** | *1/*1 | 46 (62.2%) | 70.06±29.35 | 0.41 | 137.81±78.61 | 0.73 |
| | *1/*2 | 13 (17.6%) | 70.34±31.8 | | 142.52±83.39 | |
| | *2/*2 | 1 (1.4%) | 80.4 | | 132.4 | |
| | *1/*3 | 12 (16.2%) | 65.22±27.36 | | 120.19±58.27 | |
| | *2/*3 | 2 (2.7%) | 110.12±44.99 | | 200.35±90.41 | |
| **CYP2C19** | *1/*1 | 57 (77%) | 69.32±31.29 | 0.81 | 138.92±82.79 | 0.44 |
| | *1/*2 | 11 (14.9%) | 75.33±26.55 | | 133.94±51.52 | |
| | *2/*2 | 6 (8.1%) | 73.46±22.22 | | 129.27±39.56 | |
| **C3435T** | CC | 14 (18.9%) | 71.67±27.46 | 0.96 | 146.53±78.94 | 0.84 |
| | CT | 37 (50%) | 69.65±31.22 | | 132.71±66.22 | |
| | TT | 23 (31.1%) | 71.3±29.8 | | 139.38±89.93 | |
| **G2677T/A** | GG | 22 (29.7%) | 71.68±27.43 | 0.94 | 155.72±81.13 | 0.4 |
| | GT | 34 (45.9%) | 71.91±32.96 | | 121.62±58.38 | |
| | TT | 13 (17.9%) | 69.2±30.74 | | 144.92±107.52 | |
| | GA | 3 (4.1%) | 59.69±6.36 | | 115.32±18.34 | |
| | TA | 2 (2.7%) | 60.18±31.33 | | 188.28±74.61 | |
| **T129C** | TT | 68 (91.1%) | 73.18±28.59 | 0.01 | 141.95±75.41 | 0.06 |
| | TC | 6 (8.1%) | 40.78±29.01 | | 85.8±64 | |

# Results

The study comprised 74 patients, mean age 39.69±14.39, of which 43 (58.1%) women and 31 (41.9%) men. The classification based on epilepsy type indicated a 62.2% frequency (46 cases) of idiopathic epilepsy and 37.8% (28 cases) of secondary epilepsy. Thirty-two patients (43.24%) were under monotherapy with VPA and 42 patients (56.76%) used VPA associated with other AEDs. The type of epilepsy or the treatment is not correlated with age, body mass index, body surface area or gender (table 2). Fifty-two patients could be divided into responders and non-responders according to ILAE 2010 criteria after a year of treatment. Twenty-eight were responders and 28 non-responders.

Statistically significant differences in the VPA doses, but not in VPA concentrations were observed in the patients receiving single-drug versus multidrug antiepileptic therapy, i.e. higher dosing was used in patients receiving multidrug therapy. No statistically significant differences were observed between the means of doses or concentrations of the idiopathic epilepsy group vs. secondary epilepsy group.

Statistically significant differences in the VPA doses used were observed in responders versus non-responders i.e. higher doses were used in non-responders.

The mean VPA plasmatic level was 70.55±29.78 $mg \cdot L^{-1}$. Most of the patients (62.16%) had therapeutic levels of VPA, between 50 and 100 mg·L-1. The distribution of the patients is represented

below (figure 1). There are no statistically significant differences between the mean plasma concentrations in responders and non-responders. Using the dose-adjusted-VPA-concentrations, we observed a significant difference with lower values for the non-responder group (Table 3).

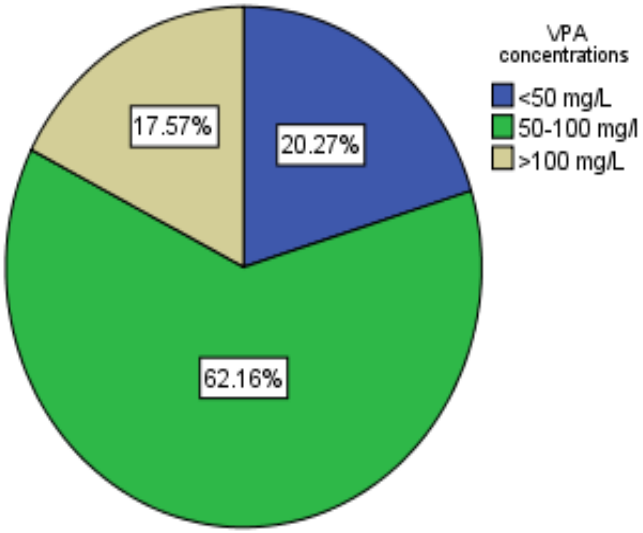


Figure 1. The distribution of VPA concentrations

The frequencies of genotypes for CYP2C9, CYP2C19, ABCB1 C3435T, ABCB1 G2677T/A and ABCB1 T-129C, were noted and compared with the expected frequencies under (Table 4). No deviations from the law Hardy-Weinberg equilibrium were founded in the population studied for ABCB1 C3435T, ABCB1 G2677T/A, ABCB1 T-129c, CYP2C9. Instead we observed a highly significant deviation for CYP2C19 ($p < 0.001$). CYP2C19 genotypes studied were those that include mutations *2 and *3, but were not discovered any mutant allele *3 CYP2C19 in the studied population.

The presence of allele C for 129 determines a statistically significant decrease in VPA plasmatic concentrations to lower than therapeutic values, but other observed polymorphisms for ABCB1 C3435T, G2677T, and CYP2C19 do not significantly influence the VPA plasmatic concentrations or the dose-adjusted-VPA-concentrations. However, the CYP2C9 *2/*3 genotype increases VPA concentrations to higher than therapeutic values (but not statistically significant) (Table 4).

## Discussions

In this cohort study we correlated pharmacokinetic VPA data with clinical and genetic characteristics (polymorphisms of ABCB1 and CYP2C9, CYP2C19) in epileptic patients.

A fifth of the patients in the study had VPA plasma concentrations lower than the minimum therapy values of 50 mg·L-1, but only one non-responder (3.5% of the total number of non-responders) had very low VPA plasma concentrations (2.06 mg·L-1). In the other 5 non-responding patients with plasma concentrations under 50 mg·L-1, plasma concentration values were at approximately 40 mg·L-1 (close to minimum therapeutic concentration). However 28 patients were classified as non-responder. Therefore we can assume that the mechanisms that cause resistance to these patients are more complex than the simple failure to attain therapeutic concentrations. In fact, 3 non-responders actually have supratherapeutic concentrations. As, statistically, there's no significant difference between the mean plasmatic concentrations at responders and non-responders, we assumed that, in the population we studied, the mechanism of resistance is independent of VPA concentrations.

The difference in doses of VPA used for monotherapy and polytherapy can be explained by the fact that in the course of establishing the required dosage, the doses of AEDs are gradually increased before inserting a new antiepileptic.

For the genes codifying microsomal enzymes CYP2C9 and CYP2C19 we obtained higher values of VPA concentrations for heterozygous CYP2C9 *2/*3, but without obtaining statistical significance. No genetic polymorphism studied for CYP2C19 did significantly alter VPA concentrations. Some studies (Ho et al 2003) had demonstrated an association between presence of allele *3 CYP2C9 and higher plasma concentrations of valproate and obtaining a hepatotoxic metabolite 4-ene-valproate, but not confirmed in other studies. A study of 287 patients with epilepsy (Jiang et al, 2003) receiving valproate showed that genotype CYP2C19 *2/*3 and CYP2C9 *3 significantly influence the therapeutic concentration of valproate.

In our study we found that the two most commonly studied ABCB1 polymorphisms in other studies, ie C3435T and G2677T/A did not affect VPA concentrations, confirming previous studies (Haerian et al 2011). For the mutations present in the promoter region T129C, generally less studied, and with no data in the literature in particular for valproate, we observed significantly lower concentrations of VPA for TC genotype (40.78±29.01 mg·l-1) compared to wild homozygotes, TT genotype (73.18±28.59 mg·l-1). No mutant CC genotype was observed in the studied population. Given the low group and low frequency of mutations T-129C, a further research is desirable. Considering that some AED's are substrates, but also inductors of glycoprotein P expression (Tan et al 2010), it is a difficult job to determine in which sense in established the influence.

In the last decade, a number of clinical pharmacogenetics studies have been conducted regarding the associations of ABCB1 genotype with the pharmacokinetic and pharmacodynamics of antiepileptic drugs. A meta-analysis of 11 trials (Bournissen et al 2009) who studied the influence of the mutation C3435T on refractory epilepsy, showed no differences in the frequency of mutations in the population refractory and all those who respond to treatment, but no analysis on drug concentration.

## Conclusion

In our study we found no significant differences between different genetic groups in VPA concentration, except for ABCB1 T129C TC heterozygotes, who reduced VPA concentrations.

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