Allele Frequency of Carbamazepine Major Efflux Transporter Encoding Gene ABCB1 C3435T among Javanese-Indonesian Population

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Abstract

BACKGROUND: Genetic variations in ABCB1 gene that encodes P-glycoprotein, the main transporter in the efflux of carbamazepine (CBZ) from the brain cells, can lead to pharmacodynamic and pharmacokinetic variability. Polymorphism of C3435T is widely known to cause protein overexpression that contributes to an increased risk of CBZ resistance.

AIM: This study determined the allele frequency distribution of ABCB1 C3435T gene in healthy subjects of the Javanese population as a major ethnic group in Indonesia.

METHODS: This cross-sectional study involved 100 healthy volunteers who fulfilled the inclusion criteria. The genotype analysis to detect polymorphism in the targets employed the polymerase chain reaction-restriction fragment length polymorphism method with 5'-TGCTGGTCCTGAAGTTGATCTGTGAAC-3' as the forward primer and 5'-ACATTAGGCAGTGACTCGATGAAGGCA-3' as the reverse primer. The frequency of subjects with C allele in CBZ resistance.

RESULTS: The frequency of subjects with C allele in ABCB1 C3435T gene reached 53%, higher than that with T allele.

CONCLUSION: This finding was nearly the same as that in studies of the populations in China, Turkey, and four countries in the South European continent. It is recommended to conduct further research on the correlation between C3435T polymorphism and CBZ dose variability to provide a comprehensive approach to epilepsy management in patients receiving CBZ.

Introduction

Epilepsy is the most prevalent chronic neurological disorder that affects at least 50 million people globally. It is characterized by periodic and unexpected seizures [1]. The prevalence in developing countries is higher than in developed countries; for example, the prevalence of epilepsy in Indonesia ranges between 5 and 74 per 1000 people. The best therapy in the management of epilepsy hitherto is using antiepileptic drugs (AEDs) [2].

Carbamazepine (CBZ) is a tricyclic compound used as the first-line AED for focal seizures, secondary generalized seizures, and tonic-clonic seizures [2]. CBZ is not only effective but also relatively inexpensive, making it listed in the AED monotherapy choices of the National Formulary since 2013 and available up to primary health-care facilities [3]. However, in addition to the risk of allergic reactions, CBZ is an AED with a narrow therapeutic range and often causes variations in pharmacokinetics and clinical response. Such variations occur due to polymorphism in the protein-encoding gene that plays a role in bioavailability and clinical response [4]. A number of pharmacogenetic studies of CBZ have been conducted to analyze genetic variants that strongly correlate with the variability of pharmacokinetics, clinical response, and adverse drug reactions (ADR). Regarding the polymorphism of HLA-B*1502 allele with the hazardous side effect named Stevens-Johnson Syndrome [5], research has been performed by involving the Indonesian population, with a frequency of mutant variant of 11.6% [6].

In addition to ADR risk, therapy failure due to CBZ resistance becomes another serious issue. It is estimated that approximately 30–40% epileptic patients experience AED resistance that leads to uncontrolled seizures despite the use of CBZ within the therapeutic
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Open Access Maced J Med Sci. 2020 Jul 20; 8(A):406-413.

The dose range [7], [8]. Furthermore, the maintenance dose of epileptic patients in monotherapy reaches 10-fold variety, indicating a wide interpatient variability of clinical response [9]. Among the contributing factors is the genetic polymorphism in the major CBZ efflux transporter named P-glycoprotein (P-gp) which is also expressed in the blood-brain barrier (BBB) [10]. Various studies have proved that the genetic variations in ABCB1 C3435T gene as a P-gp encoder lead to CBZ resistance. A number of studies involving epileptic patients in Chinese, Japanese, and Caucasian populations found a positive correlation between such polymorphism and CBZ resistance or variations in CBZ plasma concentration [11], [12], [13]. Therefore, this study aims to determine the allele frequency distribution of ABCB1 C3435T gene among the Javanese population, the largest ethnic group in Indonesia.

Pharmacogenetic understanding and studies of epilepsy therapy can provide important basic information for the development and implementation of genetic screening in making a decision on epilepsy therapy as well as become the basis for patient individualized medicine. This study is a section of prospective research on AED pharmacogenetics among the Indonesian population with epilepsy. Analysis of genetic variants in the target P-gp encoding gene is important to provide information on the genetic variation profile among the Indonesian population of which implications for individual therapeutic dose and clinical response to CBZ use can be further examined.

Methods

Research subjects

The DNA was extracted from 3 ml blood of 100 healthy respondents aged 18–23 years. The category of respondents was those from Javanese ethnic group identified based on their three previous generations. This study has obtained ethical clearance from the Ethics Committee of the Faculty of Medicine of Universitas Islam Indonesia with the protocol No. 35/Ka.Kom.Et/70/KE/XII.

Genotyping

Genotyping of ABCB1 C3435T was conducted through the polymerase chain reaction (PCR) method using 5’-TGC TGG TCC TGA AGT TGA TCT GTG AAC-3’ as the forward primer and 5’-ACA TTA TGA AGT GAC TCG ATG AAG GCA-3’ as the reverse primer followed by restriction fragment length polymorphism. PCR conditions for amplification included initial denaturation at 95°C for 2 min, 35 denaturation cycles at the same temperature for 30 s, annealing at 55°C for 30 s, extension at 72°C for 30 s, and final extension at 72°C for 5 min. The amplification products were visualized using agarose gel electrophoresis with 1.5% agarose concentration at 100 volts for 30 min. The PCR products (248 bp) were digested using MboI enzyme that identified and cut [GATC sequence in the amplicon. The digestion of amplification products yielded 16 bp, 60 bp, and 172 bp fragments of CC genotype, 16 bp, 60 bp, 172 bp, and 232 bp of CT genotype, and 16 bp and 232 bp of TT genotype.

The genotype and allele frequencies were determined based on the data of previous studies [11], [12], [13], [14] that used Hardy–Weinberg’s law as follows [15], [16]:

\[
\text{Genotype frequencies} = \frac{\text{Total number of alleles in the population}}{\text{Number of CC individuals}} + \frac{\text{Number of CT individuals}}{\text{Total number of individuals}}
\]

\[
f(C) = \frac{2 \times \text{Number of CC individuals}}{2 \times \text{Total number of individuals}} + \frac{\text{Number of CT individuals}}{2 \times \text{Total number of individuals}}
\]

\[
f(T) = \frac{2 \times \text{Number of TT individuals}}{2 \times \text{Total number of individuals}} + \frac{\text{Number of CT individuals}}{2 \times \text{Total number of individuals}}
\]

\[
f(C): \text{C allele frequency}
\]

\[
f(T): \text{T allele frequency}
\]

Results and Discussion

A total of 100 healthy respondents of Javanese-Indonesian descent participated in the ABCB1 C3435T gene genotyping with the same numbers of male and female respondents. The research subject characteristics are described in Table 1.

Table 1: Characteristics of the subjects in ABCB1 C3435T genotyping

| Patient characteristic | Male (50) | Female (50) |
|------------------------|-----------|-------------|
| Average age (years)    | 21.3 ± 1.2| 21.1 ± 1.4  |
| Average BMI (kg/m²)    | 22.7 ± 4.1| 21.5 ± 3.4  |
| Types of ABCB1 C3435T genotype |       |             |
| CC                     | 14       | 10          |
| CT                     | 29       | 29          |
| TT                     | 7        | 11          |
| Types of ABCB1 C3435T allele |     |             |
| C                      | 57       | 49          |
| T                      | 43       | 51          |

BMI: Body mass index.

This study found that the frequencies of genotypic variation of both male and female respondents were insignificantly different. Although it is acknowledged...
that gender and genetic variation frequencies are not correlated, P-gp expression and function indicate gender variations at the molecular level [17]. Therefore, in a pharmacogenomic study targeting polymorphism in ABCB1 genes that encode P-gp protein, in addition to employing a prospective technique and adequate sample size [18], taking comorbidity factors into account, and using other drugs of P-gp inducer or inhibitor [19], and it is necessary to involve equal numbers of male and female patients to provide more accurate data analysis and results. Men and women have differences not only in P-gp expression and function but also in CBZ clearance, with even a significant difference level, in an infusion therapy [20].

Overall, the findings showed that the frequencies of CC, CT, and TT genetic variation in ABCB1 C3435T (rs1045642) were 24%, 58%, and 18%, respectively. Research with the same polymorphism targets as this study has been widely performed by involving a variety of populations and various races (Table 2.)

The electrophoretic display of enzyme digestion for the detection of target polymorphism in this study is shown in Figure 1.

Figure 1: Electrophoretic display of genotypic variations in the target SNPs. Lane M = marker of 50 bp; lane C = negative control; lane U = undigested; lane 1 and 2 = CC homozygote/wild-type (172 bp and 59 bp); lane 3 and 4 = CT heterozygote (231 bp, 172 bp, and 59 bp); lane 5 and 6 = TT homozygote (231 bp). SNPs: Single nucleotide polymorphisms

Numerous studies (Table 2) have linked genetic variations in P-gp encoding gene ABCB1 to mRNA stability variations [10], the risk of epilepsy, CBZ resistance, and therapeutic dose requirements. A study involving 738 subjects in South India showed that ABCB1 C3435T increased the risk of mesial temporal lobe epilepsy with hippocampal sclerosis [31]. In addition, a study of 84 Chinese epileptic patients who received CBZ monotherapy and 210 Chinese patients who received CBZ for at least 1 month found that ABCB1 3435-TT had a lower CBZ plasma concentration, and the ABCB1 3435CC group showed higher CDRaz (concentration: Dose ratio, i.e., the ratio of measured CBZ concentration to the daily maintenance dose in mg/kgBW) than the 3435CT type [13], [21]. Other studies of 315 epileptic patients at the National Hospital for Neurology and Neurosurgery in London as well as 210 Japanese patients with epilepsy who were given CBZ for more than 2 years indicated different risks of CBZ resistance. The first study found that patients with CC genotype had a higher drug resistance compared to the group of TT genotype with 2.66 odds ratio (OR) and 1.32–5.38 confidence interval (CI) while the second study revealed that the TT genotype group was more prone to CBZ resistance instead (OR: 3.64, CI: 1.16–11.39) [11], [12]. Contradictory results were shown by two studies, each of which involved 97 epileptic patients with CBZ monotherapy and 174 healthy volunteers and 34 patients and 81 healthy subjects, in which no correlation was found between ABCB1 C3435T and either CBZ resistance or clinical response to AED [14], [29]. These varied results of studies that involved different ethnic groups or races should consequently consider the study of ABCB1 haplotype or diplotype that represents the functional unit of the gene [11].

The ATP-binding cassette transporter is widely known as the largest group of transmembrane transporters expressed in various tissue barriers including in the brain capillaries that construct the BBB, localized to the endothelial layer which can limit the entry of lipophilic drugs into the brain and express substances, such as β-amyloid, from neuroparenchyma. P-gp pushes xenobiotics from the intracellular part back to the capillary lumen, thus maintaining BBB integrity and reducing drug accumulation in the cerebral region. Since P-gp transporter is highly expressed in BBB, the polymorphism in ABCB1 gene as a P-gp encoder that influences the level of expression and function can directly affect the brain uptake as well as extrusion of AEDs, including CBZ. P-gp overexpression has been proven to play an important role in a pharmacoresistant incidence in epilepsy through decreased drug concentrations in the brain even though with a plasma therapeutic concentration [53].

Since P-gp is extensively expressed not only in BBB but also in various body tissues including in small intestine and large intestine, adrenal glands, liver, kidney, placenta, and capillary endothelial cells of testes, P-gp also plays a role in the absorption, distribution, and excretion of numerous drugs as its substrates, and its function can be influenced by the presence of inhibitor drugs. Anumber of studies have also found the influence of the target polymorphism in this study on pharmacokinetic variations, clinical response, and risk factors of cancer. C3435T polymorphism has also been proven to cause variations in the concentrations, dose requirements, and clinical response of the drugs that function in the central nervous system, such as phenobarbital, opioids, and aripiprazole [22], [36], [44]. Similarly, some studies found a significant influence of such polymorphism on
The mutant allele frequency of ABCB1 C3435T in different ethnic populations

| Population/ethnicity | Sample size | Genotype frequencies n (%) | Findings | References |
|----------------------|-------------|----------------------------|----------|------------|
| Javanese, Indonesian | 100         | 24 (24.00) 58 (58.00) 18 (18.00) | The mutant allele frequency of ABCB1 C3435T (47.4%) was lower than that of C allele | The present study |
| Chinese              | 84          | 30 (35.71) 39 (46.43) 15 (17.86) | T allele was found at 41.1%. This allele correlated with the decreased plasma concentration of CBZ in Chinese patients with epilepsy | Meng et al. (2011) [13] |
| Turkish              | 97          | 29 (29.90) 56 (56.70) 13 (13.40) | T allele frequency reached 41.8%. There was no significant correlation between MDR1 (C3435T) polymorphism and CBZ resistance among patients with epilepsy in Turkey | Ozgon et al. (2008) [14] |
| Japanese             | 210         | 70 (33.33) 92 (43.81) 48 (22.86) | The mutant allele frequency of C3435T (44.8%) was lower compared to that of C allele. Epileptic patients with T allele and mutant TT variant genotype were more likely to experience CBZ resistance among Japanese patients with epilepsy | Seo et al. (2006) [11] |
| Caucasian            | 315         | 73 (23.17) 169 (53.66) 73 (23.17) | The frequency of T allele was identical with that of C allele in ABCB1 C3435T. If compared to patients with antiepileptic drug resistance, those with antiepileptic drug resistance had CC genotype in ABCB1 3435S as opposed to TT genotype | Siddiqui et al. (2003) [12] |
| Chinese              | 210         | 68 (32.38) 112 (53.33) 30 (14.29) | T allele frequency was 41.0%. The study found that ABCB1 c.3435C>T was significantly associated with the ratio of CBZ concentration to dose from CBZ and its primary metabolites in Chinese patients with epilepsy | Zhu et al. (2014) [21] |
| Chinese              | 112         | 45 (40.18) 49 (43.75) 18 (16.07) | The mutant allele frequency of C3435T (37.9%) was lower than that of C allele. If cancer patients with TT genotype in ABCB1 suffered pain, they required a higher dose of opioid compared to those with CC/CT type | Gong et al. (2013) [22] |
| Han Chinese          | 292         | 103 (35.28) 151 (51.71) 38 (13.01) | T allele frequency was found at 38.9%. The ABCB1 rs1045642 gene did not correlate with the therapeutic response of antidepressants (both selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) in Han Chinese patients with depression | Shang et al. (2019) [23] |
| Han Chinese          | 185         | 74 (40.00) 82 (44.32) 29 (15.68) | T allele was 37.8%. Genotype variation in rs1045642 did not influence the efficacy of etanercept in Han Chinese patients with ankylosing spondylitis | Yan et al. (2017) [24] |
| Han Chinese          | 236         | 58 (24.58) 47 (19.91) 131 (55.51) | T allele was 37.8%. Genotype variation in rs1045642 did not influence the efficacy of etanercept in Han Chinese patients with ankylosing spondylitis | Zhao et al. (2019) [25] |
| Taiwanese            | 112         | 29 (25.89) 52 (46.43) 31 (27.68) | T allele was found at 50.9%. The baseline score of Hamilton Depression Rating Scale and that of week 6 in antidepressant therapy were insignificantly different among the ABCB1 C3435T genotypic variance of Taiwanese patients with major depressive disorder | Chang et al. (2015) [26] |
| Chinese              | 152         | 55 (35.72) 73 (47.40) 26 (16.88) | The mutant allele frequency of C3435T was higher than that of C allele. No significant difference was found in the estimation of MDR1 haplotype frequency between Japanese healthy subjects and patients with CRC as well as ESCC | Komoto et al. (2006) [27] |
| Turkish              | 54          | 19 (35.19) 22 (40.74) 13 (24.07) | T allele was found at 44.4%. The study found that the distributions of CC genotype and C allele in ABCB1 3435C/T were significantly different between Turkish patients with major depressive disorder and healthy subjects (n=70). However, ABCB1 C3435T polymorphism did not influence the clinical response to citalopram | Ozbey et al. (2014) [28] |
| Iranian              | 115 (34 patients, 81 healthy subjects) | 24 (20.67) 58 (50.43) 33 (28.70) | Contrary to our findings, the mutant allele frequency of C3435T (53.9%) was higher than that of C allele. The haplotype frequency estimation (including ABCB1 C3435T) did not indicate any significant difference between patients and the control group | Hosseini et al. (2018) [29] |
| Egyptian             | 220 (120 patients, 110 healthy subjects as control group) | 26 (11.82) 141 (64.09) 53 (24.09) | T allele frequency was at 56.1%. The CT genotype in MDR1 gene 3435T correlated with the poor clinical outcomes in Egyptian pediatric patients with acute lymphoblastic leukemia | Talaat et al. (2018) [30] |
| South Indian         | 460 patients | 24 (5.22) 245 (53.26) 191 (41.52) | Different from our findings, the mutant allele frequency of C3435T (65.5%) was higher than that of C allele. There was no significant difference in the dose of sufentanil for Han Chinese patients who suffered pain due to lung cancer | Balan et al. (2014) [31] |
| Romanian and Hungarian | 465; 503 healthy subjects | 48 (26.67) 26 (23.01) 6 (12.50) | There was a significant difference in the T allele frequency of MDR1 between Roman population (48.2%) and Hungarian people (52.7%). The T allele frequency in our study was found to be comparable with that of Roman population | Sipely et al. (2011) [32] |
| Polish               | 171 (71 patients, 100 healthy subjects) | 37 (21.64) 76 (44.44) 58 (33.92) | T allele distribution was at 56.1%. 1236T-2677G-3435T haplotype could provide a protective effect against bullous pemphigoid | Rychlik-Sych et al. (2018) [33] |
| Polish               | 90          | 15 (16.67) 43 (47.78) 32 (35.55) | T allele distribution was at 56.1%. ABCB1 C3435T polymorphism could provide a protective effect against bullous pemphigoid | Jelen et al. (2015) [34] |
| Romanian             | 74          | 14 (18.92) 37 (50.00) 23 (31.08) | T allele frequency was 56.1%. ABCB1 C3435T polymorphism did not influence the plasma concentration of valproate or dose adjustment with reference to valproate concentration among Romanian patients with epilepsy | Sabin et al. (2016) [35] |
| Croatian             | 60          | 16 (26.67) 31 (51.66) 13 (21.67) | Similar to our finding, this study also found a lower T allele frequency (47.5%) as opposed to that of C allele. C3435T polymorphisms in ABCB1 gene influenced the concentration ratio of phenobarbital in serum/cerebrospinal fluid among Croatian patients with idiopathic primary generalized epilepsy who received phenobarbital monotherapy | Basic et al. (2008) [36] |
the pharmacokinetics of antiviral atazanavir and the clinical outcomes of antemether-lumefantrine antimalarial regimen [37], [45] as well as the chemotherapy clinical outcomes in pediatric patients with leukemia [30], [39]. Furthermore, C3435T rs1045642 polymorphism has even been proven to correlate significantly with amiodipine efficacy and safety, patients’ blood pressure after kidney transplantation, and the safety of dabigatran as a thrombin inhibitor [40], [42], [43]. Not only associated with pharmacogenomics because of their function as part of cellular defense mechanism, but C3435T polymorphism also has a significant clinical correlation as a predisposition to depressive disorders [28], [34], [38]. A similar finding was also found in a study of haplotype involving such polymorphism with the risk of colorectal and esophageal cancer and in a systematic review and meta-analysis regarding the genetic susceptibility to multiple myeloma [27], [41].

These relatively high frequencies of C3435T mutant allele among the Javanese-Indonesian population require further studies. This is in accordance with the lacking involvement of the Indonesian population in new drug development for a drug selection approach, availability of more appropriate therapeutic doses, and health promotion strategies to prevent cancer among vulnerable subject groups.

**Conclusion**

The findings in the study of ABCB1 rs1045642 C>T allele frequencies among healthy volunteers of Javanese-Indonesian ethnic group become a novelty.
in the preliminary study of CBZ pharmacogenetics study that has never been conducted. The results indicate that the frequency of subjects with T allele in ABCB1 C3435T gene was lower than that with C allele, reaching 47%. Further research is recommended to analyze the correlation between such polymorphism and their implications for pharmacokinetic variability as well as CBZ resistance.

Acknowledgment

The authors thank the Ministry of Research, Technology, and Higher Education of the Republic of Indonesia and the Directorate of Research and Community Services of Universitas Islam Indonesia for funding the research.

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