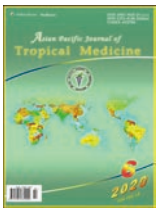

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Effect of *ABCB1* 3435C>T transporter gene polymorphism on plasma efavirenz concentration in HIV-1 infected Thai adults

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ABSTRACT

Objective: To investigate the influence of *ABCB1* polymorphisms on the plasma level of efavirenz in Thai adult cases infected with HIV-1.

Methods: A single nucleotide polymorphism of *ABCB1* 3435C>T (rs1045642) in the gene encoding *ABCB1* was genotyped using real-time PCR-based alleles in 149 HIV-infected Thai adults receiving efavirenz treatment. Plasma concentrations of efavirenz were measured by high-performance liquid chromatography 12 hr after administration. The relationship between plasma efavirenz concentrations and *ABCB1* 3435C>T polymorphisms was analyzed.

Results: Logistic regression analysis showed no significant predictors of high plasma efavirenz concentration in relation to age, gender, body weight, CD4 count and plasma HIV-1 RNA, blood biochemical parameters, antiretroviral duration or *ABCB1* 3435C>T polymorphisms, except for height (*OR*=0.902, 95% *CI:* 0.835-0.973) (*P*<0.05). The minor allele frequency of *ABCB1* 3435C>T was 0.446. The frequency of the heterozygous mutant *ABCB1* 3435C/T was 53.02% (*n*=79), *ABCB1* 3435T/T homozygous mutant was 18.12% (*n*=27) and the wild type *ABCB1* 3435C/C genotype was 28.86% (*n*=43). The overall median plasma concentration of efavirenz in 149 HIV-infected Thai cases was 2.41 mg/L [IQR: (1.46-4.12) mg/L]. The plasma concentration of efavirenz was higher in cases with *ABCB1* 3435T/T homozygous mutant [2.73 mg/L, IQR: (2.02-4.19) mg/L] and *ABCB1* 3435C/T heterozygous mutant [2.29 mg/L, IQR: (1.41-4.28) mg/L] genotypes compared to the wild type *ABCB1* 3435C/C homozygous [2.1 mg/L, IQR: (1.37-3.53) mg/L]. However, there was no statistically significant difference in the efavirenz concentration between the different genotypes (*P*>0.05).

Conclusions: There is no statistical significance for a tendency toward higher plasma efavirenz concentration in the *ABCB1* 3435T/T and *ABCB1* 3435C/T genotypes. No parameters of physiological characteristics in this study except for height were found to be predictors of high plasma efavirenz concentration in Thai HIV-1 infected cases.

KEYWORDS: Transporter gene; *ABCB1* 3435C>T; Efavirenz; HIV-1; Thai

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) infection is a global problem and has affected the Thais in different parts of Thailand[1]. HIV has been found to be co-infected with other viruses

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(*e.g.*, hepatitis)[1,2]. People with HIV are at an increased risk of cancer, while HIV cases receiving cancer treatment require careful monitoring for potential drug interactions and toxicity, particularly for the prevention of opportunistic infections[3]. Highly active antiretroviral therapy (HAART) is used to treat HIV-1 infection, lowering the amount of HIV circulating in the blood, thus allowing partial restoration of immune system function. Efavirenz, a non-nucleoside reverse transcriptase inhibitor is used as a HAART for the treatment of HIV-1 infection. Efavirenz has been combined with the popular HIV drug Truvada, which consists of tenofovir and emtricitabine. This combination provides the simple HAART in a single tablet that effectively suppresses HIV replication in most cases, increases medication adherence, and minimizes toxicity[4]. The preferred therapeutic range for plasma efavirenz concentrations is 1.0-4.0 mg/L[5]. Below 1 mg/mL, the plasma level has been associated with treatment failure in an efavirenz-based regimen[6]. The level above 4.0 mg/L has been associated with an increased risk of side effects and central nervous system toxicity[7,8]. Many antiretroviral drugs approved by the Food and Drug Administration, including efavirenz, are affected by the multidrug transporter P-glycoprotein (P-gp), encoded by the *ABCB1* gene. *ABCB1*, the 209.6 kb ATP-binding cassette gene family containing 29 exons, located on chromosome 7q21.12, has about 50 members[9]. Currently, there are more than eight common single nucleotide polymorphisms in the protein-coding region of *ABCB1*, which are 1236C>T (rs1128503), 2677G/A>T (rs2032582), c.3435C>T (rs1045642), 1659G>C (rs2235012), 781A>G (rs36008564), 239C>A (rs9282565), 1199G>A (rs2229109), and 1795C>T (rs2235036), where multiple alleles have been reported. The *ABCB1* 1236C>T allele that occurrs in exon 13, does not result in an amino acid changes, but it can affect the expression of *ABCB1* through the use of codon[10]. The *ABCB1* 2677G>T/A allele results in a change from serine to alanine or threonine at residue 893, but the effect of changes in protein function is uncertain, although it has been associated with virological failure[11]. The effect of changes in protein function of the *ABCB1* 1659G>C (a synonymous), *ABCB1* 781A>G (Ile261val), *ABCB1* 239C>A (Ala80Glu), *ABCB1* 1199G>A (Ser400Asn), and *ABCB1* 1795C>T (Ala599Thr) is also uncertain. The *ABCB1* c.3435C>T variant is commonly known to be associated with reduced expression of P-gp[12]. Previous studies in other ethnic groups on the effect of *ABCB1* c.3435C>T polymorphisms on the variability in plasma efavirenz concentrations are still unclear[13,14]. However, current data on the association of plasma levels of efavirenz and other genetic markers have been reported in HIV-1 infected Thai adults[15,16]. In addition, there are no data reporting this variant of single nucleotide polymorphism in Thai adults infected with HIV-1. This study aims to evaluate the effect of *ABCB1* 3435C>T polymorphisms on plasma levels of efavirenz in Thai adults infected with HIV-1 and to explore the clinical significance of single nucleotide polymorphisms.

2. Materials and methods

2.1. Study design and sample size calculation

The sample size of Thai HIV-infected cases was calculated to assure a 95% confidence interval based on the following formula: $n=Z^2_{\alpha}pq/d^2$, where the value of the 95% confidence interval ($Z_{0.05/2}$) (two tails) is 1.96. The frequency of *ABCB1* c.3435T allele (T=0.37) as previous described was used to calculate in this study[17]. At least 138 cases were recruited from the sample size calculation with 20% of the of the test allowance error.

2.2. Written informed consent and ethical approval

Written informed consent to participate in the study was provided in accordance with the guidelines of the Declaration of Helsinki 2008. This study was approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand (EC_590777 No. MURA2016/517).

2.3. Patient samples

A total of one hundred and forty-nine cases of Thai adults infected with HIV-1 being treated with efavirenz at Bamrasnaradura Infectious Diseases Institute, Thailand, were recruited for this study. The inclusion criteria for this study were: 1) All HIV-infected participants, aged 18 years or older, without opportunistic infections, 2) Subjects who firstly received antiretroviral and 3) Subjects who started the triple therapy regimen of tenofovir (300 mg), lamivudine (300 mg) and efavirenz (600 mg). Cases that received concomitant treatment and potentially had affected efavirenz pharmacokinetics were excluded. All subjects took the drug regimen at bedtime. The plasma efavirenz concentration in a mid-dose was determined at 12 wk after the initiation of antiretroviral therapy. A five milliliter of venous blood was collected in a steady state in an EDTA tube before administration and was submitted to the Laboratory for Pharmacogenomics and Personalized Medicine at Ramathibodi Hospital, Mahidol University for the *ABCB1* 3435C>T (rs1045642) genotyping. Samples were centrifuged at 3 000 rpm for 15 min. The genomic DNA was isolated for genotyping. Steady state plasma samples were stored at -20 ℃ for 12 hr after administration until further analysis.

2.4. *ABCB1* 3435C>T genotyping

The *ABCB1* 3435C>T polymorphism was investigated with HapMap (http://www.hapmap.org) data on Japanese and Han Chinese populations. The 5' nuclease chain reaction assay of the allele-specific Taqman® MGB probe with the PCR Viia™ 7 system in real time (Applied Biosystems®, CA, USA) was used with pre-defined *ABCB1* 3435C>T primers (assay ID: C_7586657_20, rs1045642) as previously described[17]. A probe was labeled with fluorogenic VIC dye that detects the sequence of allele 1; the second probe was labeled with a fluorogenic FAM dye that detects the sequence of allele 2. Each mixture of 20 μL of PCR contained 4 μL of genomic DNA (5 ng/μL), 10 μL of Taqman® Genotyping Mastermix, 1 μL of allele-specific Taqman® MGB probe and sequence-specific primer kit and 5 μL of DNase-free of H_2O. The thermal cycler program was set up as follows: at 95 ℃ for 10 min, 50 cycles repeated at 92 ℃ for 15 sec and 60 ℃ for 90 sec. The allelic discrimination plot was analyzed using Viia™ 7 software (Applied Biosystems®, CA, USA).

2.5. Measurement of efavirenz plasma levels

The validated isocratic method high-performance liquid chromatography and reverse phase with ultraviolet detection at 245 nm was used to measure the plasma concentration of efavirenz, as previously described[18]. A total of 300 μL of plasma samples pretreated with acetonitrile were injected into an Agilent 1100 high-performance liquid chromatography machine. An Omnispher C18 analytical column (150.0 mm×4.6 mm ID/particle size 5 μm) (Varian, CA, USA), a Chromquard RP guard column and a mobile phase consisting of 10 mM KH_2PO_4 pH 3.1: acetonitrile (50: 50, v/v) were used. Version 4.1 of ChromQuest Software was used to process the sample's peak heights. The average accuracy of 102% to 105% and the coefficient of variation <5% were established. The relationship between the plasma efavirenz concentration and the *ABCB1* 3435C>T polymorphism was analyzed.

2.6. Statistical analysis

All data were entered, edited and analyzed using the SPSS software for Windows (version 16.0; SPSS Chicago, IL). Genotype distributions were tested for the Hardy-Weinberg equilibrium using exact tests under a 95% exemption call rate. The data were summarized using medians and interquartile ranges (IQR) for continuous variables and frequencies and proportions for categorical variables. The relationship between the plasma efavirenz concentration and genetic polymorphism was assessed by the Kruskal-Wallis test. The Mann-Whitney U-test was used to compare efavirenz concentrations between two genotypes. Furthermore, the association between factors related to HIV infection (age, sex, duration of HIV infection, history of treatment, CD4 count, plasma HIV-1 RNA) and efavirenz concentration was analyzed using the logistic regression model (cases were divided into a plasma efavirenz concentration >4 mg/L and ⩽4 mg/L). Statistical significance was defined as P value <0.05.

3. Results

3.1. Efavirenz plasma concentration in HIV-infected Thai adults

The characteristics of 149 HIV-1 infected cases are shown in Table 1. The overall average plasma efavirenz concentration 12 hr after administration was 2.41 mg/L (IQR 1.46-4.12 mg/L). There were 100 cases (67.11%) in the therapeutic range (1 to 4 mg/L). There was a large inter-individual variation in plasma levels of efavirenz in 49 cases (32.89%), ranging from <1 mg/mL (efficacy cut-off value) in 11 cases (7.38%) to >4 mg/L (toxicity cut-off value) in 38 cases (25.50%).

Table 1. Characteristics of HIV-1 infected cases enrolled in this study (n=149).

Characteristics	Value
Age (years)	37.39±8.54
Gender [n, (%)]	
Male	116 (77.85%)^
Female	33 (22.15%)^
Body weight (kg)	54.64±9.46
CD4 cell count (cells/mm^3)	42 (17-109)#
Plasma HIV-1 RNA (Log copies/mL)	5.76 (5.37-6.22)#
Hemoglobin (g/dL)	10.76±1.77
BUN (mg/dL)	10.26±4.56
Serum creatinine (mg/dL)	0.73±0.19
Direct bilirubin (mg/dL)	0.34±0.37
Total bilirubin (mg/dL)	0.59±0.41
ALP (mg/dL)	147.37±128.32
AST (U/L)	46.92±30.56
ALT (U/L)	37.01±25.27
Cholesterol (mg/dL)	180.11±42.35
TG (mg/dL)	161.43±63.19
HDL (mg/dL)	111.64±38.65
LDL (mg/dL)	47.73±21.30

CD4: cluster of differentiation 4; BUN: blood urea nitrogen; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT; alanine aminotransferase; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein. #Data are expressed as median (IQR); ^data are expressed as [n, (%)]; others, mean±SD.

Table 2. Predictors of high plasma efavirenz concentration in 149 Thai HIV-infected cases.

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value
Age	1.012 (0.970-1.057)	0.578	-	-
Gender				
Male	1.090 (0.444-2.676)	0.851	-	-
Female	0.917 (0.374-2.252)	0.851	-	-
Body weight	0.961 (0.922-1.002)	0.063	-	-
Height	0.950 (0.898-1.004)	0.069	0.902 (0.835- 0.973)	0.008
CD4 cell count	0.999 (0.995-1.005)	0.936	-	-
Plasma HIV-1 RNA	1.000 (0.999-1.000)	0.373	-	-
Hemoglobin	1.025 (0.834-1.263)	0.809	-	-
BUN	0.991 (0.910-1.078)	0.826	-	-
Serum creatinine	1.695 (0.239-12.039)	0.598	-	-
Direct bilirubin	1.198 (0.463-3.101)	0.709	-	-
Total bilirubin	0.900 (0.358-2.267)	0.824	-	-
ALP	1.000 (0.997-1.003)	0.845	-	-
AST	1.005 (0.994-1.017)	0.345	-	-
ALT	1.001 (0.987-1.016)	0.877	-	-
Cholesterol	1.008 (0.999-1.017)	0.089	-	-
TG	1.006 (0.999-1.011)	0.055	-	-
HDL	1.010 (0.999-1.020)	0.064	-	-
LDL	0 .994 (0.976-1.013)	1.012		
Time ARV	0.995 (0.879-1.126)	0.935	-	-
ABCB1				
3435C>T	1.370 (0.793-2.367)	0.259	-	-
C/T (*vs*. C/C)	1.281 (0.524-3.127)	0.587	-	-
T/T (*vs*. C/C)	1.889 (0.637-5.597)	0.251	-	-

CD4: cluster of differentiation 4; BUN: blood urea nitrogen; ALP: alkaline phosphatase; ARV: antiretroviral therapy; AST: aspartate aminotransferase; ALT; alanine aminotransferase; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

3.2. ABCB1 3435C>T *allele frequency and relationship between efavirenz plasma concentration in HIV-infected Thai adults*

This study found that the frequency of the heterozygous mutant C/T genotype was 53.02% (*n*=79), *ABCB1* 3435T/T or homozygous mutant T/T genotype was 18.12% (*n*=27) and the wild type *ABCB1* 3435C/C genotype was 28.86% (*n*=43). The *ABCB1* 3435C>T polymorphism was subsequently analyzed under the Hardy-Weinberg equilibrium. The frequency of the minor "T" allele of *ABCB1* 3435C>T was 0.446. The median plasma concentration of efavirenz in Thai HIV-infected cases with *ABCB1* 3435T/T was 2.73 mg/L (IQR 2.02-4.19 mg/L), *ABCB1* 3435C/T genotype was 2.29 mg/L (IQR 1.41-4.28 mg/L) and *ABCB1* 3435C/C wild type was 2.10 mg/L (IQR 1.37-3.53 mg/L). There was no statistical significance in the efavirenz concentration between the different genotypes (P>0.05).

3.3. The association of multiple factors and plasma efavirenz concentration

The logistic regression analysis showed that there was no association of plasma efavirenz concentration with any parameter of physiological characteristics, such as age, gender, body weight, CD4 count and plasma HIV-1 RNA, blood biochemical parameters, duration of HIV infection or *ABCB1* 3435C>T polymorphisms. Treatment history, except for height, which was considered as a predictor of high plasma efavirenz concentration (*OR*=0.902, 95% *CI:* 0.835-0.973) in Thai HIV-1 infected cases, with significant difference (P<0.05) (Table 2).

4. Discussion

Our report demonstrated the high frequency of *ABCB1* 3435T allele in HIV-1 infected Thai adults. The allele is 53.02% of *ABCB1* 3435C/T heterozygous, 18.12% of *ABCB1* 3435T/T homozygous and 28.86% of homozygous wild type *ABCB1* 3435C/C. The distribution of the *ABCB1* 3435C>T polymorphism in this study seems to be smaller than other groups previously reported, such as 49.0% of Japanese cases[20], 46.6%-54.0% of Chinese cases[21,22] and 63.2%-64.0% of Indian cases[23,24], 54.9% of Caucasian cases[25], and 84.0% in Maasai[26]. However, the distribution is greater than some other groups, such as 11.0%-21.0% of African cases[19,21,25] and 37.3% of Taiwanese cases[27]. Genetic variation in the *ABCB1* gene is known to alter mRNA stability or splicing activity[28]. *ABCB1* 3435C>T difference of polymorphism in the mRNA levels of the P-gp

messenger[29], synonymous at 1, 145th residue with the reduction in the expression of the P-gp[12,30]. The penetration of the drug in the target cells was observed in the alteration of the expression of P-gp and its function. Then the difference in single nucleotide polymorphism in *ABCB1* 3435C>T could impact the response to antiretroviral therapy in different populations with variability in plasma efavirenz concentration[12–14]. We observed that the efavirenz plasma concentration in the trend of the *ABCB1* 3435T/T [2.73 mg/L, IQR (2.02-4.19) mg/L] and *ABCB1* 3435C>T [2.29 mg/L, IQR (1.41-4.28) mg/L] were superior to the homozygous wild type *ABCB1* 3435C/C [2.10 mg/L, IQR (1.37-3.53) mg/L]. Although the findings tend to suggest that *ABCB1* 3435C>T is probably considered the predictive marker of efavirenz outcomes, but there was no statistically significant difference (P>0.05). Besides, our results are previous reports of lower concentrations of nelfinavir and efavirenz associated with the *ABCB1* 3435T/T polymorphism[12,24], and data from 126 HIV infected cases in South India with the highest values of plasma efavirenz concentration in the wild type *ABCB1* 3435C/C genotype [(5.22±5.32) mg/L], followed by *ABCB1* 3435C>T [(3.5±1.83) mg/L] and *ABCB1* 3435T/T [(2.48±1.29) mg/L][24]. The data revealed that inter-individual variations in plasma efavirenz concentrations may be due to an indirect effect of genetic variations in the *ABCB1* gene. Thus, further studies with larger sample are needed to verify the benefits of treatment in HIV-infected patients in the future.

The other parameters of physiological characteristics of this study, such as age, gender, body weight, CD4 count and plasma HIV-1 RNA, biochemical parameters in the blood, duration of HIV infection, or treatment history, showed no significant association with plasma efavirenz concentration in the cases of Thai HIV-infected (P>0.05), except for height (OR=0.902, 95% CI: 0.835-0.973) (P<0.05).

In conclusion, although our results among Thai HIV-1 treated with efavirenz demonstrated a tendency towards a higher plasma concentration of efavirenz in cases with the *ABCB1* 3435T/T and *ABCB1* 3435C>T genotypes, but there is no significant statistic with the wild type *ABCB1* 3435C/C. All parameters of physiological characteristics in this study, except height were not found to be predictors of high plasma efavirenz concentration in Thai HIV-1 infected cases. Further studies with a larger scale of sample sizes are recommended for verification.

Conflict of interest statement

We declared that we have no conflict of interest.

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Authors' contributions

S.B and C.S. developed the concepts. S.B., N.K., R.S., M.C. and A.P. performed the analytical experiment. S.B., N.K., R.S., M.C., W.M. and A.P. performed the data curation. S.B. performed the validation and supervised the project. S.B. and N.K. contributed to the first draft version of the manuscript. S.B., V.N., M.C. and M.P. contributed to the final version of the manuscript.

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