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Measuring the Overall Genetic Component of Nevirapine Pharmacokinetics and the Role of Selected Polymorphisms: Towards Addressing the Missing Heritability in Pharmacogenetic Phenotypes?

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Abstract

Objective—Nevirapine is an important component of highly active antiretroviral therapy used in the treatment of human immunodeficiency virus infection. There is considerable variation in the pharmacokinetics of nevirapine and this variation can impact the efficacy and toxicity of nevirapine. While some of this variation can be attributed to environmental factors, the degree to which heritability influences nevirapine pharmacokinetics is unknown. This study aims to estimate how much variation in nevirapine pharmacokinetics is due to genetic factors and to investigate the contribution of selected polymorphisms to this variability.

Methods—Two doses of immediate-release nevirapine were administered to European (n=11) and African American (n=6) subjects recruited from the Research in Access to Care in the Homeless (REACH) cohort. A repeated drug administration (RDA) method was then used to determine the relative genetic contribution (r_{GC}) to variability in nevirapine AUC_{0-6h} . Nevirapine plasma levels were quantified using LC-MS/MS. Patients were also genotyped for selected polymorphisms in candidate genes that may influence nevirapine pharmacokinetics.

Results—A significant r_{GC} for nevirapine AUC_{0-6h} was found in Europeans ($p = 0.02$) and African Americans ($p = 0.01$). A trend towards higher nevirapine AUC_{0-6h} for the *CYP2B6* 516TT (rs3745274; Q172H) genotype was observed in European Americans ($p = 0.19$).

Conclusions—This study demonstrates that there is a significant genetic component to variability in nevirapine pharmacokinetics. While genetic variants such as *CYP2B6* polymorphisms attributed to some of this variation, these data suggest that there may be additional genetic factors that influence nevirapine pharmacokinetics.

Keywords

HIV; Nevirapine; Pharmacogenetics; Pharmacokinetics; CYP2B6

Introduction

The importance of understanding the role of genetics in variation in pharmacokinetics and pharmacodynamics has been recognized since the 1950s [1–3]. Twin studies have historically been used to determine the heritability of genetic diseases and traits; these studies have also been used to determine the heritability of pharmacodynamic and pharmacokinetic parameters [4]. While twin studies are a useful technique to determine genetic contributions to pharmacokinetic variation, it can be impractical to use twins in pharmacogenetic studies due to difficulty in recruitment and the need to expose them to drugs. A statistical technique that was specifically developed to address this issue is the repeated drug administration (RDA) method, which uses repeated administrations of a drug to the same individuals to compare the within-subject and between-subject variation in pharmacokinetic parameters [5]. This comparison can be used to quantify the relative genetic contribution to variations in pharmacokinetic parameters of a drug. While the RDA method is useful in determining whether pharmacokinetic or pharmacodynamic parameters of a drug have strong genetic components, it may vary with the route of administration, dose of drug or patient population [5]. Additionally, while one pharmacokinetic parameter for a given drug may have a strong relative genetic component, other parameters may be more highly influenced by environmental factors than by genetic factors [6]. Repeated drug administration has successfully been employed to characterize the genetic contribution to variability in pharmacokinetic parameters of several drugs, including erythromycin, midazolam and metformin [7,8]. However, the genetic contribution to pharmacokinetic parameter variability for many drugs is still unknown.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor widely used as a component of antiretroviral therapy in the treatment of human immunodeficiency virus (HIV) [9]. Nevirapine exhibits considerable variability in its pharmacokinetic properties; however, only part of this variability can be explained by environmental factors and concomitant conditions [10]. Variation in nevirapine pharmacokinetics can lead to reduced efficacy, increased viral resistance and increased toxicities [11]. Nevirapine is metabolized to its primary metabolite 3-hydroxynevirapine by *CYP2B6* [12]. The *CYP2B6* 516G>T and *CYP2B6* 983T>C variant alleles have a significant effect on nevirapine plasma levels and the *CYP2B6* 516T allele has also been associated with increased recovery of CD4+ T-cell populations in pediatric patients following initiation of nevirapine-containing antiretroviral therapy [13–15]. Additionally, *ABCB1* 3435C>T has been associated with protection against nevirapine-induced hepatotoxicity and increased nevirapine concentrations in cerebral spinal fluid [16,17]. Despite evidence that nevirapine pharmacokinetics are influenced by specific

polymorphisms, there has not been a study conducted to quantify the relative genetic contribution to variability in nevirapine pharmacokinetics.

This study uses the repeated drug administration method to quantify the relative genetic contribution to variability in nevirapine pharmacokinetics. A significant relative genetic contribution to variation in nevirapine exposure was shown in two ethnic populations. The contribution of *CYP2B6* 516G>T and *ABCB1* 3435C>T to variability in nevirapine pharmacokinetics was also investigated.

Materials and Methods

Study Design and Subjects

Subjects were recruited from the Research in Access to Care in the Homeless (REACH) cohort as previously described [18]. Study participants are marginally housed HIV positive individuals living in San Francisco. Nineteen patients were recruited to participate in a pharmacokinetic study where subjects receiving 200 mg nevirapine twice daily consented to pharmacokinetic blood sampling. All subjects were on therapy at least four months and were concomitantly receiving two nucleoside reverse transcriptase inhibitors. Subjects were presumed to have reached steady state concentrations. Blood samples were drawn at 0, 1, 2, 3 and 6 hr post-dose. The time between the two measured doses varied from 13 days to 173 days. European American (n=11) and African American (n=6) patients were included in this study. Ethnicity was self reported and verified through genotyping of 112 ancestry informative markers and analysis using the STRUCTURE program [19–21]. The study was approved by the University of California Institutional Review Board and all subjects provided written informed consent prior to participation.

Nevirapine Quantification

Plasma was prepared from blood samples by centrifugation and stored at -80°C until analysis. Nevirapine was extracted using Oasis HLB SPE columns (Waters Corp., Milford, MA) and plasma concentrations were quantified by LC/MS/MS analysis as described by Mistri *et. al* [22]. Briefly, each 0.5 mL plasma aliquot was heated for 1.5 hrs at 56°C to inactivate HIV-1 virus and then spiked with 25 μL of 20 μM metaxolone (Toronto Research Chemicals, Toronto, Ontario) in methanol, which served as an internal standard. SPE columns were equilibrated with 1 mL methanol followed by 1 mL distilled water. Samples were then loaded on the column and washed with 1 mL of 2 mM ammonium acetate followed by 1 mL of water. Samples were eluted in 1 mL mobile phase (80:20 acetonitrile:water, 0.1% acetic acid) and a 5 μL aliquot was injected onto a 5 μm Hypersil BDS C18 column, $50 \times 4.6 \mu\text{m}$ (Thermo Fisher Scientific, Waltham, MA). The flow rate into the API4000 mass spectrometer (AbSciex, Framingham, MA) was 0.2 mL/min and nevirapine retention time was 1.7 min. The parent ion (267.2 m/z, amu) and product ion (226.2 m/z, amu) were monitored at Q1 and Q3, respectively. Nevirapine standard curves were linear from 50–5000 ng/mL ($r^2 > 0.9$). Assay accuracy was between 100.3% and 112.9% relative standard deviation. Assay precision ranged from 8.2 – 18.5% CV.

Genotyping

Genomic DNA was extracted from whole blood samples. Genotyping of polymorphisms of interest (*CYP2B6* 516G>T and *ABCB1* 3435C>T) was accomplished using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). TaqMan assays were used to genotype *CYP2B6* 516G>T (rs3745274, Assay ID: C___7817765_60) and *ABCB1* 3435C>T (rs1045642, Assay ID: C___7586657_20). Genotypes were called with ABI Sequence Detection System software (version 2.1; Applied Biosystems, Foster City, CA).

Calculation of Pharmacokinetic Parameters

Due to the long half-life of nevirapine (45 hrs), only AUC_{0-6h} was calculated [23]. AUC_{0-6h} was calculated for each dose administration using the trapezoidal rule.

Calculation of Relative Genetic Component

The genetic contribution to the variability in nevirapine AUC_{0-6h} was assessed with a modified ANOVA formula for estimating the relative genetic component or r_{GC} and 95% confidence intervals proposed by Kalow et.al. [24]:

$$r_{GC} = (SD_b^2 - SD_w^2) / SD_b^2$$

which can be rearranged as

$$r_{GC} = 1 - (1/F) \text{ where } F = SD_b^2 / SD_w^2$$

Upper and Lower Confidence intervals can be calculated as follows:

$$\text{Lower 95\% confidence interval} = F_{\text{observed}} / F_{0.025, b.d.f, w.d.f}$$

$$\text{Upper 95\% confidence interval} = F_{\text{observed}} * F_{0.025, b.d.f, w.d.f}$$

where r_{GC} represents the estimated relative genetic component, SD_b^2 is the between subjects variation, SD_w^2 is the within subject variation, b.d.f. is the between subjects degrees of freedom, w.d.f. is the within subject degrees of freedom and $F_{0.025}$ is the tabulated F statistic at the 2.5% significance level at the appropriate degrees of freedom. Due to well characterized differences in allele frequency and linkage disequilibrium patterns, European Americans (n=11 and African Americans (n=6) were analyzed separately in this study.

Statistical Methods

Statistical significance for genetic contribution to AUC_{0-6h} variability was calculated using an F-test, $\alpha=0.05$, to determine if the inter- and intra-individual variation was significantly different. One-way ANOVA, $\alpha=0.05$, was used to determine significance for the effect of genetic polymorphisms on AUC_{0-6h} values. All other calculations of p -values were obtained using two-sided t -tests or one-way ANOVA as appropriate [25]. Calculations were performed using R and Microsoft Excel [26]. All figures were produced in Prism Version 5.01 (GraphPad Software Inc., San Diego, CA).

Results

Ethnicity does not play a role in nevirapine AUC_{0–6h} variability

Since there are well characterized differences in the genetic structure and linkage disequilibrium patterns in various ethnic populations, a statistical analysis to examine any overall differences in nevirapine AUC_{0–6h} between African and European Americans was conducted. A total of 17 subjects were included in this study, 11 European Americans and six African Americans (Table 1). Median ages and concomitant medications were similar in the two ethnic groups, while the African American group had a higher proportion of females than the European American group.

Analysis of nevirapine plasma concentrations indicated very little intrasubject variability in concentrations during the six hours following drug administration, consistent with the long terminal half-life of this drug (see Figures 1 and 2, Supplemental Digital Content Figure 1). In contrast, there is considerable variation in nevirapine concentrations between individuals; three individuals in the African American and two in the European American groups never reach plasma concentrations above the minimum effective concentration (MEC) for nevirapine of 3000 µg/L [27]. Average AUC_{0–6h} did not differ between the two visits, although there was significant interpatient variability in these values (Table 1). For example, the mean AUC_{0–6h} was 22.5 mg nevirapine/L*hr (SEM = 3.81 mg nevirapine/L*hr) and 18.3 mg nevirapine/L*hr (SEM = 2.69 mg nevirapine/L*hr) for European and African Americans, respectively. There was not a significant difference in AUC_{0–6h} between the two populations (*t*-test, *p* = 0.45).

Age and sex do not play a role in the variability of nevirapine AUC_{0–6h}

To insure further analyses were not confounded by demographic factors, the effect of age and sex on nevirapine AUC_{0–6h} was examined by linear regression and *t*-tests, respectively. Age had no effect on nevirapine AUC_{0–6h} with an *r*² of 0.04. Males tended to have slightly lower AUC_{0–6h} (16.2 mg nevirapine/L*hr, SEM = 37.0 mg nevirapine/L*hr) than females (23.0 mg nevirapine/L*hr, SEM=24.2 mg nevirapine/L*hr), however this difference was not statistically significant (*p*=0.14).

There is a significant genetic contribution to variation in nevirapine AUC_{0–6h}

The relative genetic contribution to nevirapine pharmacokinetics was calculated using the RDA method described previously [5,7]. The between subject (*SD*_b²) variation in AUC_{0–6h} was about 10-fold greater than the within subject variation (*SD*_w²) in both ethnic groups (Table 2). The *r*_{GC} calculated for the European Americans and African Americans was 0.902 (95% confidence intervals 0.64–0.97) and 0.904 (95% confidence intervals 0.42–0.98), respectively. *F*-tests indicate there is a significant genetic contribution to the variability in AUC_{0–6h} in both Europeans (*p* = 0.02) and African Americans (*p* = 0.01).

CYP2B6 516G>T may influence nevirapine AUC_{0–6h}

Considering the evidence for a significant genetic contribution to the variability in nevirapine exposure, polymorphisms in candidate genes implicated in the metabolism and transport of nevirapine were tested for association with nevirapine pharmacokinetics. In

African Americans, there is a trend for increased plasma nevirapine levels in individuals carrying the *CYP2B6* 516G>T allele or the *ABCB1* 3435C>T allele (Figures 1A and 2A); however, the sample sizes are too small for formal statistical analysis (Table 2). A similar trend was observed for the *CYP2B6* 516G>T allele in European Americans, but these differences did not reach statistical significance (Figure 1B and Table 2). There was no indication of an association between the *ABCB1* 3435C>T polymorphism and nevirapine pharmacokinetics in European Americans (Figure 2B and Table 2).

Discussion

While there have been many candidate gene studies on nevirapine pharmacokinetics, this is the first study to determine the overall relative genetic influence on nevirapine pharmacokinetics. A significant relative genetic contribution to the variability in nevirapine pharmacokinetics was demonstrated in European and African Americans. This supports previous findings that have implicated polymorphisms in drug metabolism and transport genes in nevirapine pharmacokinetic variability and toxicity [14–16]. A trend consistent with previous studies of elevated plasma concentrations in subjects homozygous for the *CYP2B6* 516G>T allele was also observed [13,15].

Variability in nevirapine pharmacokinetics and toxicity has been observed since its approval for the treatment of HIV. Many candidate gene studies have confirmed that a portion of pharmacokinetic variability is due to polymorphisms in *CYP2B6* [14,28,29]. However, the variation in pharmacokinetics due to genetic versus environmental factors has never been examined. The current study demonstrates that there is a significant genetic component to nevirapine pharmacokinetics in African and European Americans. While the population examined here is small, one advantage of the RDA method is the ability to use small populations to estimate relative genetic components of drugs [6]. In our European population, we have a reasonable number of subjects to estimate a 95% lower confidence limit of ~0.65 for an r_{GC} of 0.9 [6]. This suggests that interindividual variation in nevirapine drug levels could be reduced through knowledge of a patient's genetic background. The importance of this is reflected in the observation that several patients did not reach the minimum effective concentration of nevirapine, which could lead to decreased efficacy against HIV and increased viral resistance to nevirapine. The RDA method has been successfully employed to identify drugs whose renal clearance has a strong genetic component and could also be used to identify antiretroviral drugs that are good candidates for pharmacogenomics research [8].

To further investigate the influence of genetics on nevirapine pharmacokinetics, two candidate polymorphisms were selected for study. A trend was observed towards elevated AUC_{0-6h} of nevirapine in both European and African Americans homozygous for the *CYP2B6* 516G>T polymorphism. This polymorphism has been associated with a slight decrease in hepatic protein expression and function, therefore increases in AUC_{0-6} are expected [30]. While the results in European Americans did not reach statistical significance, the analysis was limited by a small sample size and may have been confounded by unidentified environmental factors. The trend observed is consistent with other published work, which supports the need for a larger study population [14,15,31]. No association of

ABCB1 3435C>T with nevirapine exposure was observed in our study. The effect of this polymorphism on nevirapine pharmacokinetics remains controversial, with many studies not showing an effect on nevirapine plasma pharmacokinetics [13–15,29,32]. AUC_{0-6h} may not be the most appropriate pharmacokinetic parameter to observe the effects of these polymorphisms; however, due to the long half-life of nevirapine, it was not possible to calculate other pharmacokinetic parameters such as half-life or oral clearance.

The current study demonstrates that there is a significant relative genetic component to nevirapine pharmacokinetics. While *CYP2B6* polymorphisms have been attributed to some of this variation [14,15,31], this study suggests that there may be additional genetic factors that influence nevirapine pharmacokinetics. These data support additional research to discover novel genetic factors influencing nevirapine variability. Furthermore, the RDA method could also be used to study endpoints of antiretroviral drugs other than pharmacokinetic parameters, including pharmacodynamic and metabolomic endpoints [33]. Additional knowledge of genetic factors that affect nevirapine pharmacokinetics may help increase the efficacy of nevirapine in the treatment of HIV and lead to less viral resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

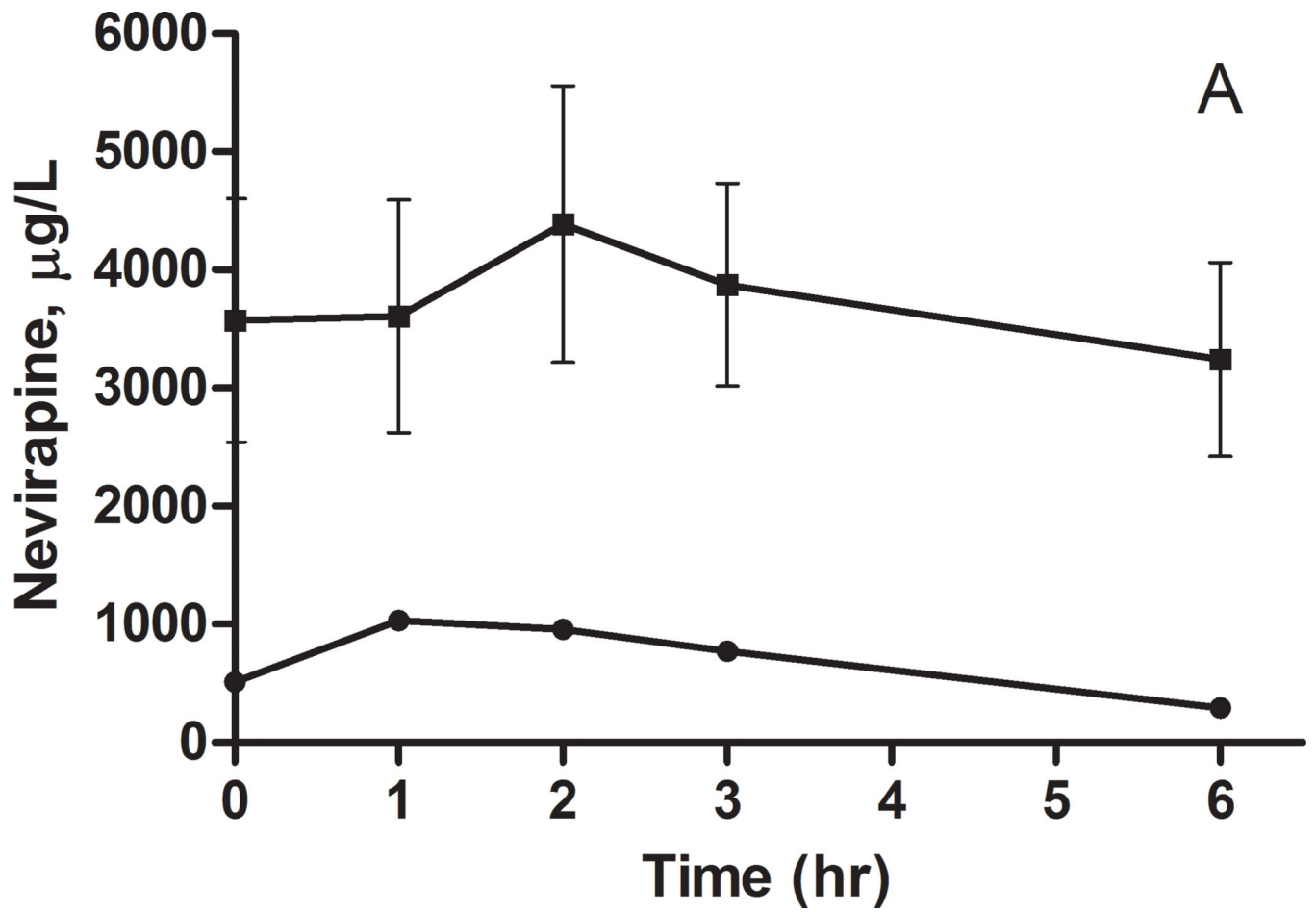
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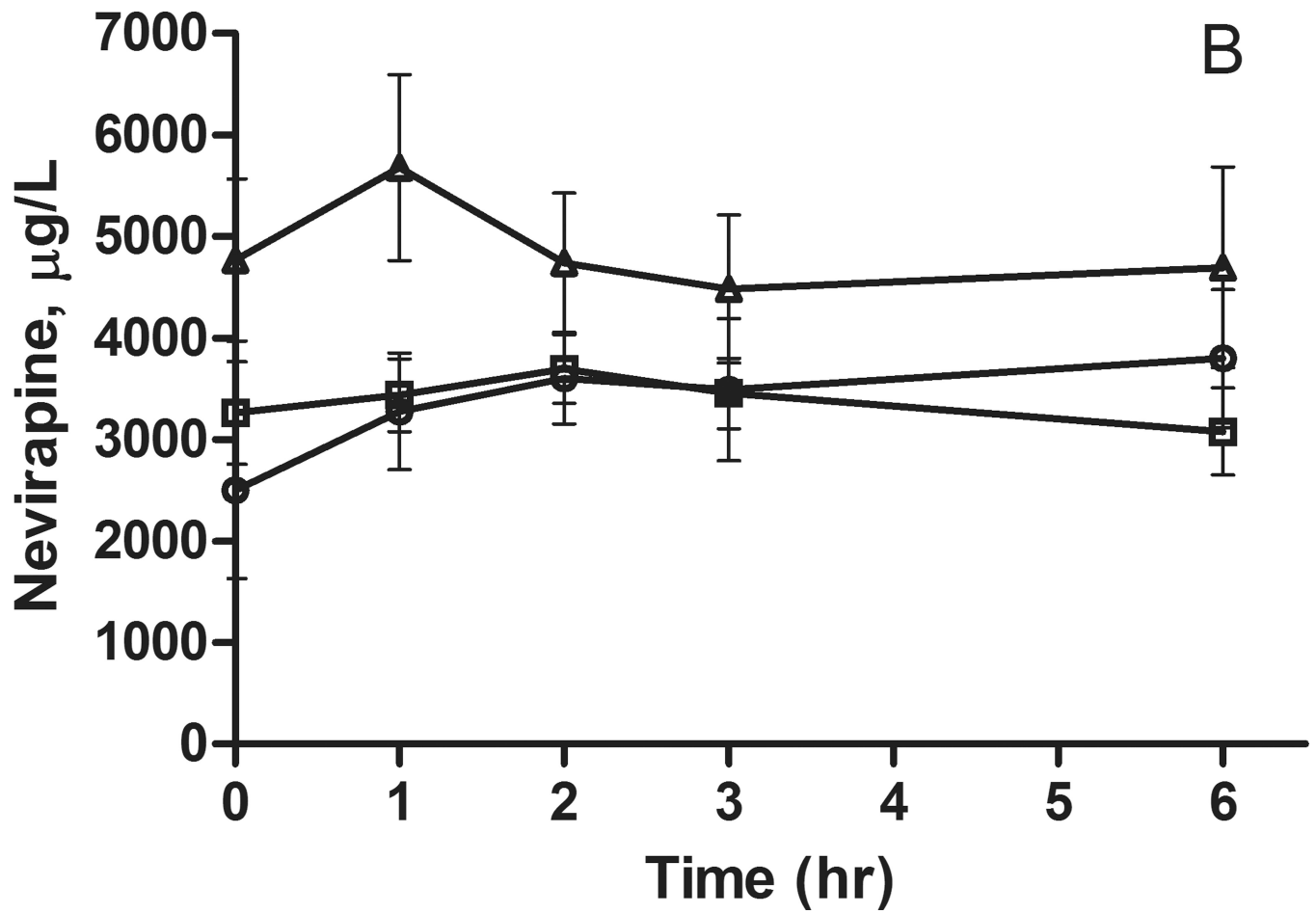
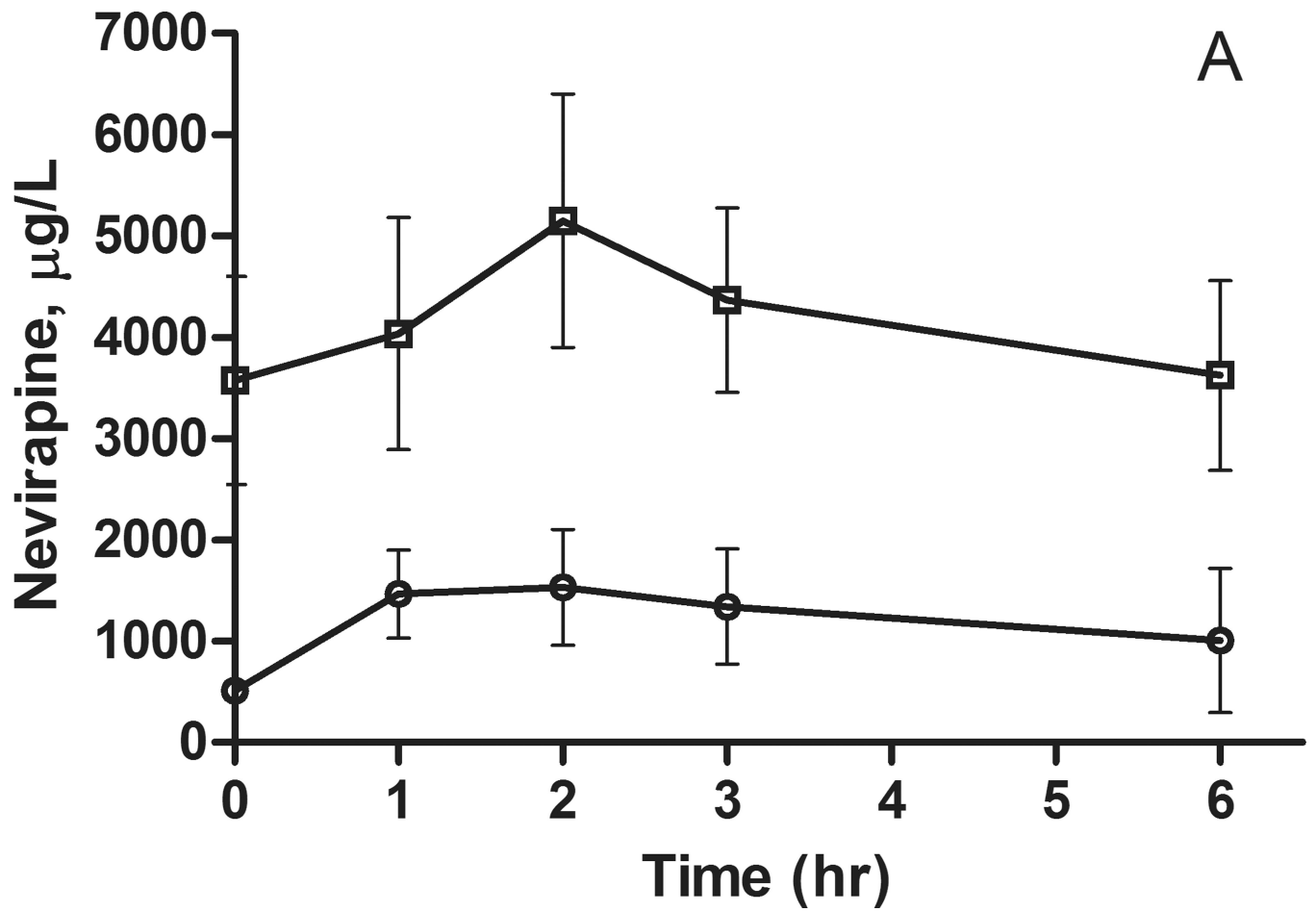


Figure 1. Nevirapine plasma concentrations following a 200 mg dose to A) African Americans and B) European Americans. The concentrations (mean \pm SEM) are stratified by *CYP2B6* 516G>T genotype: circles GG, squares GT and triangles TT.



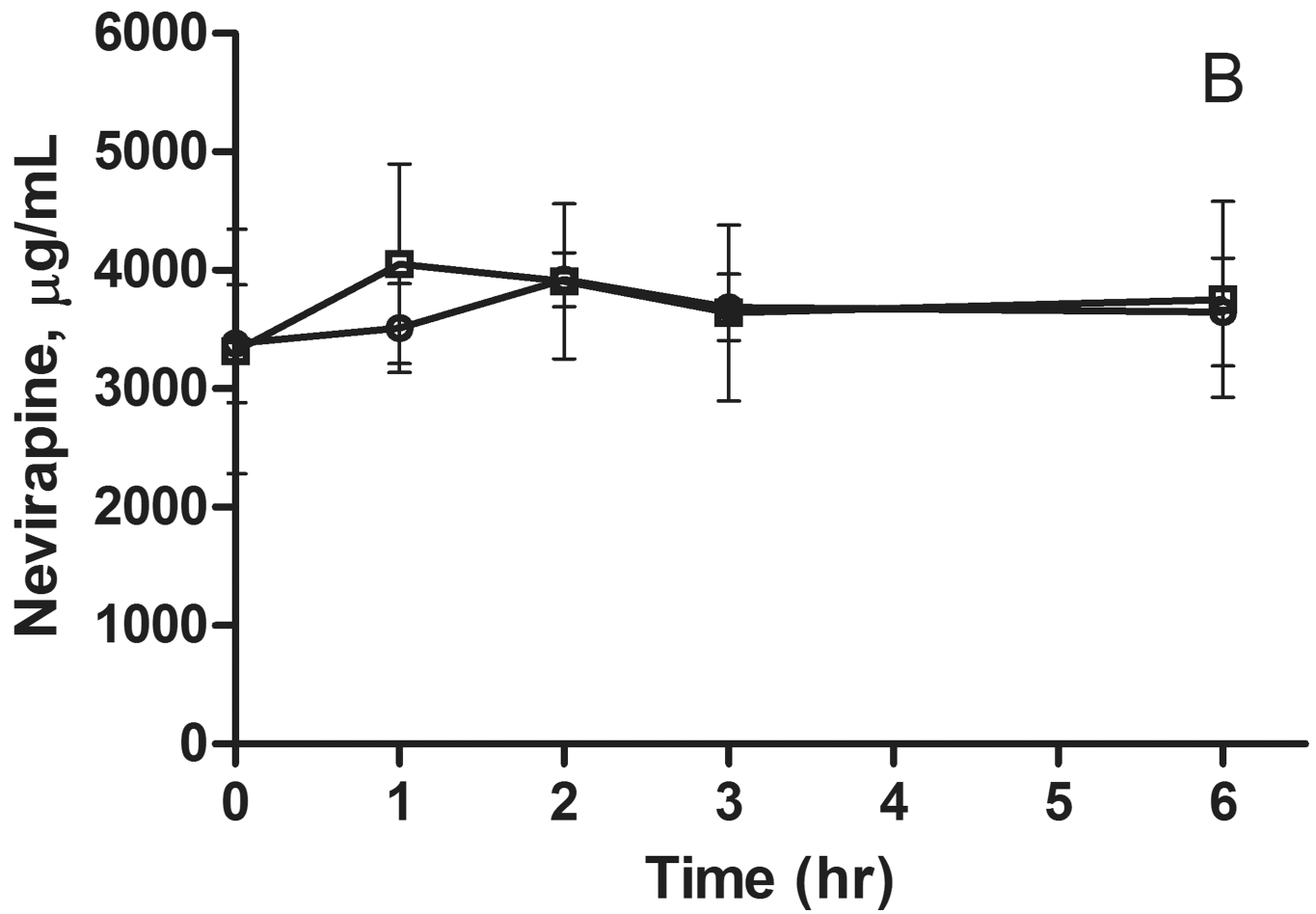


Figure 2. Nevirapine plasma concentrations following a 200 mg dose to A) African Americans and B) European Americans. The concentrations (mean \pm SEM) are stratified by *ABCB1* 3435C>T genotype: circles CC and squares CT.

Table 1Patient demographics and relative genetic contribution (r_{GC}) to nevirapine AUC_{0-6h}

		European Americans	African Americans
Sample Size	n	11	6
Gender	Male (%)	4 (36)	1 (17)
	Female (%)	7 (64)	5 (83)
Age (years)	Median	45	49
	Range	29 – 57	33 – 74
	SD_w^2	2.39	5.34
Nevirapine AUC_{0-6h} (mg/L*hr) ¹	SD_b^2	24.9	54.7
	r_{GC}^2 (95% CI)	0.904 (0.64 – 0.97)	0.902 (0.42 – 0.98)
	F	10.4	10.2
Estimated Relative Genetic Component	p	0.02	0.01

¹ SD_w^2 is within individual variation and SD_b^2 is within subjects variation.

²Estimated relative genetic component

Table 2

The effect of ethnicity and genotype on nevirapine exposure

	Ethnicity	n	Nevirapine AUC_{0-6h} (mg/L*h)^I	P
	African American	6	18.3 ± 3.81	0.45
	European American	12	22.5 ± 2.69	
	African Americans			
	GG	1	4.23	ND
	GT	5	21.2 ± 5.63	
	TT	0	-	
CYP2B6 516G>T	European Americans			
	GG	4	20.5 ± 3.16	0.19
	GT	5	20.3 ± 2.82	
	TT	3	28.8 ± 3.64	
	African Americans			
	CC	2	7.31 ± 7.97	0.17
	CT	4	23.8 ± 12.8	
ABCB1 3435C>T	European Americans			
	CC	6	22.0 ± 3.03	0.96
	CT	5	22.2 ± 3.32	

^I Mean ± SEM