ETHNICITY AND THE ECG

J. Olbertz, P. Chai, B DeGroot, M Wiedel
Celerion

ABSTRACT

Background/Aims: Over the last decade, the majority of drugs withdrawn from the market have been withdrawn due to cardiac safety concerns. This has led to increased regulatory scrutiny of cardiac safety assessment during drug development including the finalization of ICH E14 which describes the requirement for a Thorough QT/QTc (TQT) trial. In this guidance it is made clear that "Although data are limited, it is not expected that the results of the "thorough QT/QTc study" would be affected by ethnic factors." The aim of this project was to further evaluate the potential role of ethnicity on QTcB.

Methods: Data was collected from 625 healthy normal volunteers that were screened for studies conducted at MDS Pharma Services from Jan 2006-Dec 2007. Electrocardiograms (ECGs) were acquired using General Electric MAC 1200 cardiographs using version 17 of the 12SL measurement algorithm. QT values were corrected for heart rate using Bazett's correction factor (QTcB). The differences between the ethnic groups (African-American, Caucasian, and Hispanic) in QTcB and other ECG parameters were tested with the linear mixed effects model

Results: The QTcB means were 407.8, 408.3 and 406.4 msec for African-American, Caucasian, and Hispanic participants respectively. There was no statistical difference between the ethnic groups.

Conclusion: These data support the assumption that Hispanic, Caucasian, and African-American ethnicity should not have an impact on the results of the TQT trial.

INTRODUCTION

Due to withdrawal of several drugs in the last 2 decades due to association with Torsades de Pointes, a potentially life threatening arrhythmia, a Thorough QT/QTc (TQT) trial has been advocated for almost all drugs in development as outlined in the ICH E14 guidance document, "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs"[1]. The results of the TQT can have a significant impact on drug development programs. A negative TQT is defined in ICH E14 as a change in QTc in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms. A positive TQT trial can result in the requirement for more extensive and expensive ECG monitoring in later stage trials, termination of development, non-approval and/or labeling implications, all of which have a significant impact on the development program costs and future marketing efforts. Because of the implications of the TQT trial there is considerable effort that goes into planning the TQT to ensure that any changes in QT/QTc that may be observed are due to drug induced changes alone and not to other potentially controllable factors [2]. One such concern has been ethnicity of study participants. ICH E14 states that "Although data are limited, it is not expected that the results of the "thorough QT/QTc study" would be affected by ethnic factors." The aim of this project was to further evaluate the potential role of ethnicity on QTcB, QRS, QT, heart rate (HR), and PR intervals measured using standard bedside 12 lead ECG equipment with the goal of better defining the potential impact of participant ethnicity on TQT results.

METHODS

A total of 750 ECG recordings were collected from 625 healthy normal volunteers age 18-50 that were screened for studies conducted at the MDS Pharma Services site in Phoenix, Arizona from Jan 2006-Dec 2007. ECG data was acquired using General Electric MAC 1200 cardiographs at 500 samples per second. Data was acquired using clinic standard operating procedures. The QTc, QRS, QT, HR, and PR intervals were taken from a median representative beat using version 17 of the Marquette 12SL analysis program. The HR corrected QT (QTc) was calculated using Bazett's heart rate correction factor:

$$QTc = \frac{QT}{\sqrt{RR}}$$

Analysis was done to determine if there was a statistically significant difference in mean ECG parameters between ethnic groups: Hispanics (HIS), Caucasians (CAU), and African-Americans (AA). Normality was evaluated by ethnic group for the ECG parameters. The normality analysis was used to determine whether the data was skewed and identify any possible outliers. To test if there was a statistically significant difference between the least square means (p-value < 0.05), the analysis was performed with analysis of variance (ANOVA) linear mixed effects model. The ANOVA model included the terms screening group (when the subjects screened for a clinic trial) and ethnicity as fixed factors and subject nested with screening group as a random factor. The analysis was conducted with PROC MIXED in SAS®. The differences of the least square means for the pair wise comparisons between ethnicity were present along with the 95% confidence intervals of the differences.

RESULTS AND DISCUSSION

A total of 625 healthy normal volunteers were used in this analysis of 750 different ECG recordings. Of the 750 ECG recordings 27 were from African-American participants, 142 were from Caucasian participants, and 581 were from Hispanic participants. All volunteers were between the ages of 18-50. A summary of the resulting ECG data is provided in Table 1 and a summary of the differences in least square means is provided in Table 2.

In this analysis, QRS duration was found to be significantly lower in African-American relative to Caucasian participants. Whereas QTc was not significantly different from the other populations studied, suggesting that although time for ventricular depolarization may be shorter in African-Americans duration of ventricular contraction is not. The PR interval was found to be higher in the African-American relative to the Hispanic population suggesting that atrial depolarization may take longer in the African-American population.

Interestingly QT was found to be lower in the Hispanic compared to the Caucasian population and HR was significantly higher (Figures 1 and 2). As a consequence there was no difference in QTc between any of the groups (Figure 3). Bazett's correction factor was used in this analysis and is known to have shortcomings as a correction for HR particularly with very low or high HRs. In this population, HR ranged from 42-100 BPM thus over and/or under correction of QT cannot be ruled out [3]. However results of this study are corroborated by other reports in which no difference in QTc interval was observed in elderly female Hispanic, Caucasian and African-American populations although in this case the authors did see a significant increase in QTc in Asian women compared to the other ethnic groups [4].

Although there may be little observable difference in mean QTc between the populations used for this analysis, in order to better evaluate the impact of ethnicity on the outcome of the TQT the next step will be to evaluate the response of participants in these different ethnic groups to treatment with moxifloxacin. Some limited data are available suggesting that response to intravenous moxifloxacin is similar in African-American and Caucasian participants [5]. Although there are other examples of ethnic differences in sensitivity to a drug's QT prolonging effects. For example, in one investigation, it was shown that Caucasians were more sensitive than Koreans to the QT prolonging effects of quinidine [6]. Differences in QT response to medications would also not be too surprising in light of reports that there are ethnic differences in cardiac ion channel gene variants and expression [7, 8]. Thus, additional research is still needed to evaluate if there are ethnic differences in sensitivity specifically to orally administered moxifloxacin in order to further evaluate the potential impact on TQT outcomes.

		Difference	Std Err
QT			
	AA-CAU	1.1	6.7
	AA-HIS	10.7	6.3
	CAU-HIS	9.6	3.2
QTc			
	AA-CAU	-0.4	3.4
	AA-HIS	1.5	3.2
	CAU-HIS	1.9	1.6
HR			
	AA-CAU	0.2	2.3
	AA-HIS	-2.2	2.1
	CAU-HIS	-2.4	1.1

Table 1

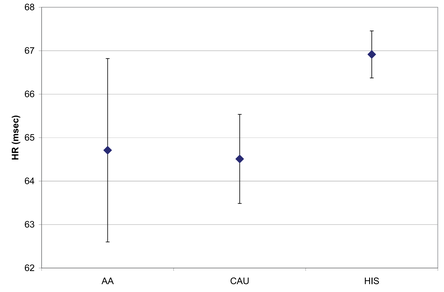
Values represent the difference and standard error in least square means between African-American and Caucasian populations (AA-CAU), African-American and Hispanic populations (AA-HIS), and Caucasian and Hispanic populations (CAU-HIS).

		POP	AA	CAU	HIS
QRS		94.1	*90.1	*94.4	93.1
	UL		93.4	96	93.9
	LL		86.7	92.7	92.2
HR		66	64.7	*64.5	*66.9
	UL		68.9	66.5	68
	LL		60.6	62.5	65.9
PR		151.9	*160.5	153.4	*150.6
	UL		167.4	157	152.4
	LL		152.7	149.9	148.7
QT		389.4	398.8	*397.7	*388.1
	UL		411	403.6	384.9
	LL		386.5	391.8	391.2
QTcB		404.8	407.8	408.3	406.4
	UL		414	411.3	407.9
	LL		401.6	405.3	404.8

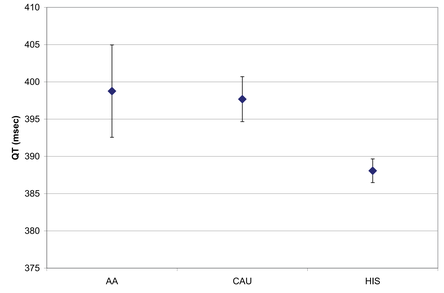
Table 2

***Differences were significant (p<0.05) between ethnic groups with similar symbols. Values represent Least Squared Means in msec and the Upper Limit (UL) and Lower Limit (LL) of the 95% confidence interval.**

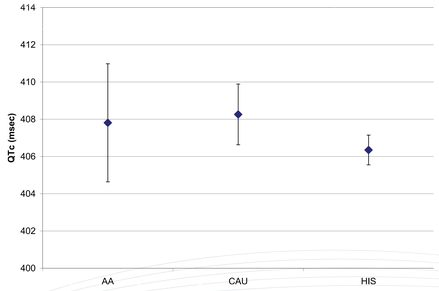
HR (mean) Fig 1



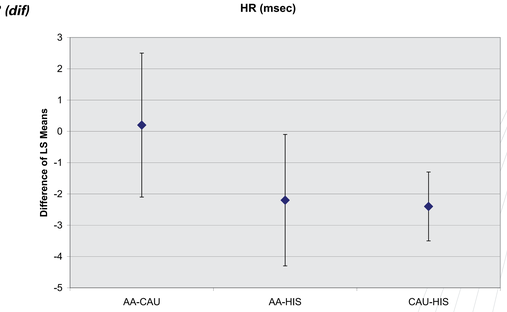
QT (mean) Fig 2



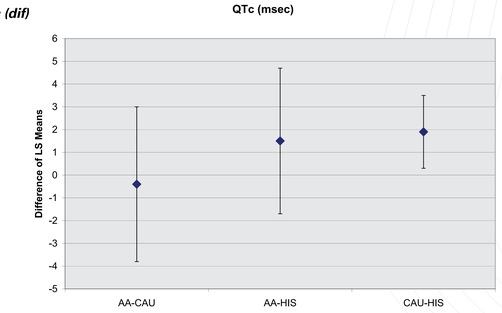
QTc (mean) Fig 3



HR (dif)



QTc (dif)



REFERENCE

1. *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs: Guidance to Industry, ICH, Editor.* 2005: Federal Registry. p. 61134-61135.
2. Malik, M., C.E. Garnett, and J. Zhang, *Thorough QT Studies: Questions and Quandaries.* Drug Saf, 2010. **33**(1): p. 1-14.
3. Hodges, M., *Rate Correction of the QT Interval.* Cardiac Electrophysiology Review, 1997. **3**(3): p. 360-363.
4. Rautaharju, P.M., et al., *Normal Standards for QT and QT Subintervals Derived from a Large Ethnically Diverse Population of Women Aged 50 to 79 Years (the Women's Health Initiative [WHI]).* The American Journal of Cardiology, 2006. **97**(5): p. 730-737.
5. Malik, M., et al., *Electrocardiographic QTc changes due to moxifloxacin infusion.* J Clin Pharmacol, 2009. **49**(6): p. 674-83.
6. Shin, J.-G., et al., *Possible interethnic differences in quinidine-induced QT prolongation between healthy Caucasian and Korean subjects.* British Journal of Clinical Pharmacology, 2007. **63**(2): p. 206-215.
7. Ackerman, M.J., et al., *Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome.* Mayo Clin Proc, 2003. **78**(12): p. 1479-87.
8. Liu, J.F., et al., *Phenotypic Variability in Caucasian and Japanese Patients with Matched LQT1 Mutations.* Annals of Noninvasive Electrocardiology, 2008. **13**(3): p. 234-241.

www.celerion.com