Investigating Ethnic Differences In QTcF Response To Moxifloxacin In A Randomized, Double-Blind Study

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BACKGROUND

A dedicated Thorough QT (TQT) study to assess the potential for a compound to induce QT prolongation is required for most drugs before approval. In most TQT studies, moxifloxacin is administered as an active control to ensure study sensitivity (Bloomfield, et al., 2008). Ethnic differences based upon varying prevalence of genetic ion channel variants result in different incidences of Congenital Long QT Syndrome, and sensitivity to drug induced QT prolongation are well documented (Kannankeril, Roden, Norris, Whalen, & George, 2005) (Arbour, et al., 2008) (Koo, Ho, & Lee, 2005) (Shin, et al., 2007) (Kapa, et al., 2009). An ethnic difference in response to moxifloxacin could have a significant impact upon TQT study design thus one of the objectives of this study was to assess whether there is an ethnic difference between Hispanic or Latino (HL) and Non-Hispanic or Non-Latino (NHNL) subjects in QT prolongation following a single dose of moxifloxacin.

METHODOLOGY

36 healthy volunteers were enrolled and 33 completed a double-blind, randomized 2-way crossover study comparing the effects of moxifloxacin (single dose of Avelox® 400 mg tablet) to matching placebo on QT corrected for heart rate using Fridericia's correction (QTcF). Subjects were stratified by gender and by ethnicity as HL or NHNL. Triplicate, 10-second, 12-lead ECG recordings were extracted from Holter recordings at 10 pre-specified time points. The mean of the triplicate values was used as the value for that time point. Baseline was the average of 3 pre-dose time point triplicate ECGs. The QT interval was measured using a previously validated highly automated method in which cardiologist review is limited to ECGs demonstrating characteristics associated with inaccurate automated measurement.

Change from baseline in QTcF (dQTcF) at each time point was described by an analysis of covariance model (ANCOVA). The analyses were performed using SAS® PROC MIXED with treatment, period, sequence, ethnicity, and interaction of ethnicity by treatment as fixed effects, subject within sequence as a random effect, and each subject's baseline value as a covariate. The effect of ethnicity on placebo-adjusted dQTcF (ddQTcF) was found by the following estimate based on least-squares means: (HL[moxifloxacin]-HL[placebo])-(NHNL[moxifloxacin]-NHNL[placebo]).

RESULTS

The group response to moxifloxacin was typical in extent and time course with peak effect of 13.4 ms at 2.5 hours. Several lower limits of the 2-sided, 90% confidence interval (CI) were greater than 5 ms confirming assay sensitivity (Figure 1). Within-subject standard deviation (SD) was 5.9 ms at peak moxifloxacin effect and 6.5 ms overall. Intra-reader variability was 2.8 ms.

The dQTcF response to moxifloxacin over time was typical with peak values at 3.5 hours post-dose for HL (17.4 ms) and at 3 hours post-dose for NHNL (15.2 ms). There were no statistically significant differences between the two groups through 12 hours post-dose (Figure 2).

Figure 1.

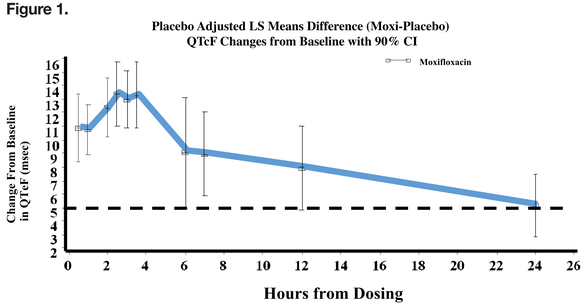
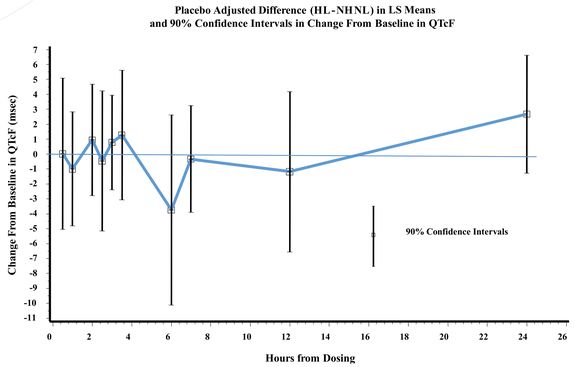


Table 1. The Effect of Ethnicity (HL-NHNL) on ddQTcF by Hour Following Dosing

Hour	Estimate of Difference (HL-NHNL) in ddQTcF (ms)	90% Confidence Interval		p-value
		Lower	Upper	
0.5	0.0	-5.06	5.09	1.00
1.0	-1.0	-4.83	2.82	0.66
2.0	0.9	-2.78	4.67	0.67
2.5	-0.5	-5.15	4.22	0.87
3.0	0.8	-2.39	3.96	0.68
3.5	1.3	-3.08	5.60	0.63
6.0	-3.8	-10.13	2.62	0.33
7.0	-0.3	-3.91	3.24	0.88
12.0	-1.2	-6.56	4.19	0.71
24.0	2.7	-1.29	6.63	0.26

HL= Hispanic or Latino
NHNL=Non-Hispanic or Non-Latino.

Figure 2.



DISCUSSION

Genetic differences in cardiac ion channel function can result in Congenital Long QT Syndrome and increased sensitivity to drug-induced QT prolongation. Generally these genetic differences are very infrequent in the population but can vary with ethnicity, causing different phenotypic expression between ethnic groups. A large study of 829 unrelated, normal individuals divided by ethnicity into Black, White, Asian, and Hispanic found only one mutation (V195L) significantly more common in Hispanics than in the other groups at about 6.7%. The functional status of this polymorphism is unknown. In an examination of the Women's Health Initiative (Rautaharju, RJ, Kadish, Larson, Hsia, & Lund, 2006) no significant difference was found in QT and QTcF between Hispanic and White women. A recent review of the large Vanderbilt Electronic Medical Record Population (Ramirez, et al., 2011) revealed no significant difference in QT or QTcB between Hispanics and Whites.

To our knowledge, our study is the first comparing the response of HL with NHNL subjects to the known QT prolonging effects of a drug. Our study confirms the observations on the lack of difference in static QT measurements between HL and NHNL and demonstrates that there is no difference in response to the QT prolonging drug moxifloxacin. This suggests that stratification by HL and NHNL subjects is not necessary for a TQT study.

CONCLUSIONS

1. No significant ethnic difference in dQTcF response to moxifloxacin was demonstrated between HL and NHNL individuals.
2. This suggests that ethnic stratification by HL or NHNL is not important in the design of a TQT.

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