Exploring Gender Differences in QTcF Response to Moxifloxacin in a Randomized, Double Blind Study

W. Wheeler[1], J. Olbertz[1], S. Azzam[1], B. DeGroot[1], E. Reinbolt[2], K. Clark[1]
[1]Celerion, [2]DataCeutics, Inc

BACKGROUND

ICH E14 mandates a Thorough QT/QTc (TQT) study for most new compounds to assess for the potential to cause QT prolongation which is associated with Torsade de Points (TdP). A positive control is administered to determine study sensitivity (ICH, 2005), usually the antibiotic moxifloxacin (Bloomfield, et al., 2008). A gender difference in moxifloxacin response could have significant effect upon TQT study design. Females have greater risk of TdP in both congenital and acquired Long QT Syndromes (Drici & Clement, 2001). Females also have longer QT intervals, greater drug-induced QT prolongation in some cases (Nakagawa, Takahashi, Taniguchi, Anan, Yonemochi, & Saikawa, 2006) and greater within subject variability (Zhang, Dmitrienko, & Luta, 2008). We looked at the effect of gender upon the QTcF response to moxifloxacin in a TQT-like study.

METHODOLOGY

36 healthy volunteers were recruited and stratified by gender into 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). 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 ECGs taken in triplicate. The QT interval was measured using a previously validated highly automated method in which cardiologist review is limited to ECGs having characteristics associated with automated measurement inaccuracies.

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, gender, and interaction of gender by treatment as fixed effects, subject within sequence as a random effect, and each subject's baseline value as a covariate. The effect of gender on placebo-adjusted dQTcF (ddQTcF) was found by the following estimate based on least-squares means: (female[moxifloxacin]-female[placebo])-(male[moxifloxacin]-male[placebo]).

RESULTS

A total of 33 subjects completed the study. A typical QTcF placebo-adjusted response to moxifloxacin was seen with group peak effect of 13.4 milliseconds (ms) at 2.5 hours (Fig 1). The lower limit of the 2-sided, 90% confidence interval (CI) was greater than 5 ms at multiple time points, confirming assay sensitivity (Figure 1). Within-subject standard deviation (SD) was 5.9 ms at peak effect and 6.5 overall. Analysis by gender revealed that females had a greater response to moxifloxacin than males at two time points, 2.5 and 3.0 hours, with peak difference of 6.4 ms at 2.5 hours (Table 1 and Figure 2).

Figure 1.

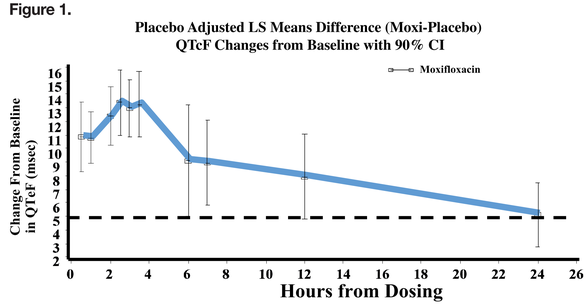
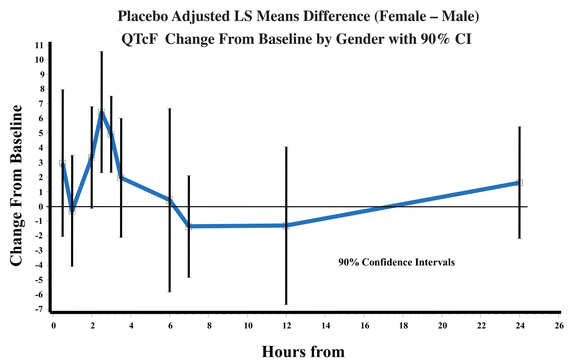


Table 1. The Effect of Gender (Female-Male) on ddQTcF by Hour Following Dosing

Hour	Estimate of Difference (Female-Male) in ddQTcF (ms)	90% Confidence Interval		p-value
		Lower	Upper	
0.5	2.9	-2.07	7.94	0.33
1.0	-0.3	-4.10	3.47	0.90
2.0	3.3	-0.15	6.79	0.11
2.5	6.4	2.28	10.54	0.01
3.0	4.9	2.30	7.52	0.00
3.5	1.9	-2.12	6.00	0.43
6.0	0.4	-5.82	6.68	0.91
7.0	-1.4	-4.85	2.10	0.52
12.0	-1.3	-6.68	4.05	0.68
24.0	1.6	-2.19	5.41	0.48

Figure 2.



DISCUSSION

We have confirmed that females have a greater response moxifloxacin induced QTcF prolongation than males. Some have suggested that TQT studies should be performed with only males to decrease variability introduced by female subjects (Dmitrienko, Beasley, & Mithcell, 2008) and thereby decrease sample size. However, the same group (Zhang, Dmitrienko, & Luta, 2008) has shown in an analysis of 4 TQT studies, that although the variance in female QT measurements would provide significantly larger sample sizes for TQT studies performed with females only vs males only, the impact of using both genders has minimal effect upon the sample size. Dmitrientko et al., also argued that if females indeed have a greater QT prolonging effect from a compound than males, supratherapeutic doses can make up for this in males. The determination of supratherapeutic dose in a TQT is often problematic. Including the more sensitive to QT prolongation female subjects would be an added safety factor in determining the QT prolonging effect of any drug. Because there is little statistical penalty for enrolling both female and male subjects it is reasonable to do so and stratify based upon gender to account for the greater effect in females.

CONCLUSIONS

1. Females have an increased sensitivity to the QT prolonging effects of moxifloxacin, as seen in some other drugs.
2. Including females in TQT studies should increase the sensitivity of TQT studies
3. TQT studies should be stratified by gender to account for the difference in QT effects.

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