QT PROLONGATION IN HEALTHY JAPANESE SUBJECTS RECEIVING MOXIFLOXACIN IN THOROUGH QT STUDIES

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Introduction

The confirmation of assay sensitivity in Thorough QT (TQT) studies is commonly assessed by the use of positive controls. Moxifloxacin, a fluoroquinolone antibacterial agent, has been widely used as a positive control in well over one hundred TQT studies. However, there are few data of QT prolongation by moxifloxacin in Japanese subjects and even less of its use as a probe to assess assay sensitivity in TQT studies. Although, the ICH guidelines state that ethnic factors are not expected to affect the results of a 'thorough QT/QTc' study and therefore are independently valid regardless of the race of the study population, there is little documented evidence to support or refute this[1]. A recent publication by Kumagai *et al*. (2011)[2] demonstrated the degree of change in QTcF but to date no pharmacokinetic (PK) or pharmacodynamic (PD) analysis has been published in Japanese and Caucasian subjects within the same trial.

Aims

This study is the first study to compare the effect of moxifloxacin (400 mg) on QTc in Japanese subjects compared to data from Caucasian subjects.

Methods

This study was an open-label, randomised, placebo-controlled, crossover trial that evaluated the effect of different meals on the QT/QTc interval of the electrocardiogram (ECG) using a single 400 mg dose of moxifloxacin. In the study, fed and fasted conditions in non-elderly healthy male and female, Caucasian (*N*=13; 7♂, 6♀) and Japanese volunteers (*N*=19; 11♂, 8♀) was used. The subject demographics for the volunteers were as follows: Caucasian mean age 25.6 ± 4 yrs, mean height 172.8 ± 8.5 cm, mean weight 65 ± 7.2 kg; Japanese mean age 27.6 ± 3.3 yrs, mean height 167.1 ± 7.1 cm, mean weight 57.9 ± 5.6 kg The study consisted of two periods, each with a baseline ECG day (Day -1) and treatment days (Day 1, Day 2 and Day 3). The two periods were separated by at least a 3 day wash-out period.

ECG recording

12-lead ECGs were recorded using a MAC1200® recorder connected via a fixed network connection to the MUSE® (Cardiology Information System). All ECGs recorded during the study were stored electronically on the MUSE information system. 12-Lead ECG recordings were made after the subjects had been resting in a supine position for at least ten minutes. The subjects avoided postural changes during the ECG recordings and clinical staff ensured that subjects were awake during the ECG recording. At each time-point, ECGs were recorded in triplicate, to reduce variance and improve the precision of measurement. The triplicates were performed at approximately one-minute intervals. In addition, 12 lead Holter ECG recordings were performed.

Data Analysis & Statistical Methods

All ECGs and their associated automated interval measurements were subsequently reviewed by qualified Cardiologists in accordance with the ICH E14 Guidance for Industry document and ICH E14 Implementation Working Group Questions and Answers document before any of the ECGs were used for the thorough ECG analysis. The manual adjudication process applied in this study is also referred to in the ICH guidance and relevant literature as "manual over read", "computer assisted" or "semi automated" ECG measurements.

For all study ECGs, the over-reading cardiologists were blinded to time, date, treatment and any data identifying the subject. All ECGs of a given subject were over read by the same cardiologist (or cardiologists in case manual adjustments of the automated measurement are necessary) using MUSE.

The following parameters on each ECG were assessed by a cardiologist using the commercially available MUSE® in its latest version:

- QT interval
- RR interval
- Heart rate (HR)
- PR interval
- Presence or absence of U-wave
- Quantitative and qualitative ECG variations

Safety Assessment

Adverse events were recorded from the first study treatments until follow-up.

Results

Effect of moxifloxacin 400 mg on QTc (fasting)

Mean QTcF was increased in subjects receiving moxifloxacin 400 mg compared with placebo. The greatest effect was observed at 4 hours (Japanese) and 2.5 hours (Caucasian) post ingestion.

- mean change QTcF [90%CI]: 17.7 [15.3, 20.1] msec (Japanese)
- mean change QTcF [90%CI]: 12.1 [8.2, 16.0] msec (Caucasian)

The maximum QTcF value at these time points were 459.1 msec and 457.9 msec for Japanese and Caucasian subjects, respectively.

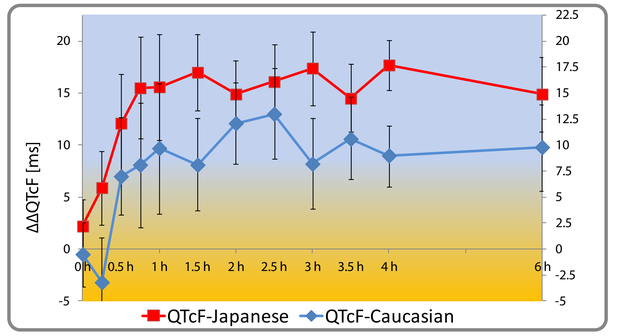

Figure 1. Effect of moxifloxacin 400 mg by race (uncorrected for weight) with confidence interval of 90%.

Pharmacokinetic parameters of moxifloxacin (400 mg)

The mean C_{max} for moxifloxacin was found to be 2.66 ± 0.74 in the Caucasian subjects and 3.15 ± 0.59 for the Japanese subjects. In addition, AUC_{0-t} was found to be 8.05 µg.hr/ml and 8.42 µg.hr/ml for Caucasian and Japanese subjects, respectively (Table 1). Plasma concentrations are shown in Figure 2.

	C_{max} (µg/ml)	AUC_{0-t} (µg.h/ml)
Caucasian	2.66 ± 0.74	8.05 ± 2.89
Japanese	3.15 ± 0.59	8.42 ± 2.47

Values are means ± SD.

Table 1. Pharmacokinetic parameters of 400 mg moxifloxacin in Japanese and Caucasian subjects.

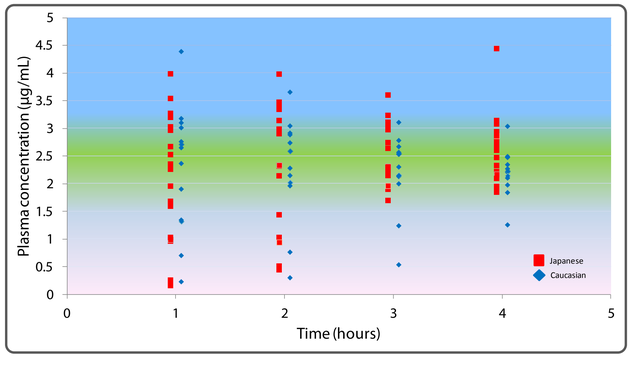

Figure 2. Individual plasma concentration of 400 mg moxifloxacin in Japanese and Caucasian subjects.

QTcF vs. PK analysis (fasting)

The relationship between QTcF and moxifloxacin plasma concentration of Japanese and Caucasian subjects in the fasted state was analysed (Figure 3). A linear increase in moxifloxacin concentration was associated with an enhancement in QTcF in both Japanese and Caucasian subjects. The difference between slopes for the two groups was not statistically significant.

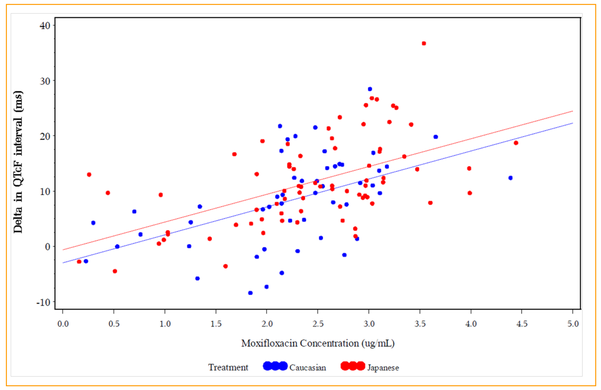

Figure 3. Relationship between QTcF interval and plasma moxifloxacin (400 mg) concentration in fasting Japanese and Caucasian subjects.

Discussion and Conclusion

ICH guidelines state that ethnic factors are not expected to affect the results of a 'thorough QT/QTc' study which are thought to be independent of the race of the study population. The pharmacokinetic data suggest that the QTcF effect following 400 mg moxifloxacin was greater in Japanese subjects compared to Caucasians. Although, ΔΔQTcF for a single dose of moxifloxacin in this study was slightly higher than previously reported (11.3±8.6)[3], our finding is consistent with the Sugiyama *et al*. (2011) study that assessed the effects of levofloxacin on QT/QTc interval in both races and showed no statistical difference in the change in QTc interval between races. Furthermore, the QTcF vs. PK relationship suggests that there was no statistical difference in the slopes between subjects. This finding is in agreement with another study that reported no difference in slopes (QTc vs. moxifloxacin) among race categories[4].

References

1. ICH E14. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhytmic Potential for Non-antiarrhythmic Drugs. International Conference of Harmonisation Step 4 Guideline, EMEA, CHMP/ICH/2/04. 25-5-2005.
2. Kumagai *et al*. Basic and Clinical Pharmacology and Toxicology.109, Supp 1: June 2011, page 102.
3. Sugiyama *et al*. British Journal of Clinical Pharmacology (2011, doi: 10.1111/1365-2125.2011.04110.x).
4. Florian *et al*. Journal of Clinical Pharmacology. 51: 1152 – 62 (2011).

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