DIURNAL PROFILE OF THE QTc INTERVAL FOLLOWING MOXIFLOXACIN ADMINISTRATION

J. Täubel [1,2] ***, G. Ferber***[3]***, S. Fernandes***[1]***, A. John Camm***[2]

[1]*Richmond Pharmacology Ltd, London, United Kingdom;* [2]*Cardiovascular and Cell Sciences Research Institute, St George's University of London, London, UK;*
[3]*Statistik Georg Ferber GmbH, Riehen, Switzerland*

Introduction

Moxifloxacin is a broad spectrum fluoroquinolone antibiotic with a well-documented and consistent QT prolongation effect, widely used in TQT studies as positive control to demonstrate the sensitivity of the assay in accordance with the ICH E14 guideline [1].

The modulation of the QT interval by diurnal factors and its dependence on time of day may also have implications on the measurement of repolarization speed in cardiotoxicity studies of investigative medical products. The importance of circadian modulators has been recognized in the quantification of the moxifloxacin drug-response relationship through pharmacokinetic (PK) QT modelling [2]. The aim of the present study was to describe the diurnal changes in cardiac repolarization, assess the impact of standardized meals on the QT interval adjusted by the Fridericia correction, and characterize the variation in cardiac repolarization duration over 24 hours following 400-mg moxifloxacin administration with periodic bedside ECG combined with continuous Holter ECG data in order to elucidate the true time course of the QTc prolongation attributable to moxifloxacin.

Methods

A post hoc analysis was performed on the 12-lead Holter data and 12-lead ECG data obtained during a TQT study published by Taubel et al, [3] which was part of a single-center, randomized, double-blind, placebo- and positive-controlled, 4-way crossover study of a novel intravenous formulation of amisulpride.

ECG data was obtained from 4 baseline and the 4 study days of a four-way crossover TQT study in 5 Japanese women, 12 Japanese men, 12 Caucasian women and 11 Caucasian men completing the study. Each assessment day in each of the four periods was preceded by a full baseline day, during which procedures were identical to the assessment day, except that no PK samples were drawn. On all study days ECGs were recorded using Mac1200 to obtain readable valid triplicates in parallel to Holter recordings using a GETEMED device. Dual electrodes ensured that both systems recorded identical electrical signals throughout. Bedside recordings were used for the TQT analysis and the 12-lead Holter data was stored for backup and future methodology research.

In all periods standardised identical meals were served. Breakfast was provided 1 hour before dose and completed 30 minutes prior to the dosing time. Lunch and dinner were served at approximately 7 and 13 hours after breakfast, respectively.

All parameters (heart rate, QT, QTcF) were extracted by averaging 3 consecutive beats generating approximately 29,000 values per 24-hour Holter record. Each mean value was compared to an average of the 22 subsequent values (moving average) in order to exclude outlier values. If the difference between the value and the averaged value was greater than 5%, then it was assumed that the value was implausible and therefore was excluded from analysis. The 24-hour period was then divided into 144 intervals of 10 minutes. The values were averaged over the 10-minute periods.

Results

During the day significant decreases in QTcF were observed consistently after breakfast and lunch with a less pronounced shortening after dinner, which is also shorter in duration. The maximum QTc effect occurred 3-4 hours after the start of each meal (Fig 1A). A steep increase in mean HR was observed following each meal (Fig 1B).

The 24-hour profile of moxifloxacin displayed a persisting QTcF prolonging effect at the end of the Holter recordings, 24 hours after dose administration. This effect was well above the threshold of concern (Figs 3A and 4 A).

The Holter QTcF-measurements after moxifloxacin administration followed the pattern observed in the conventional analysis of the bedside ECG-derived QTcF values (Fig 4).

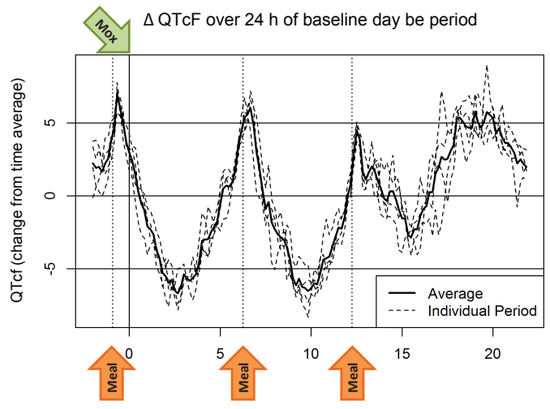

Fig 1: Time course (change from individual average baseline) of QTcF and HR on Day -1 by period. For each subject the average over the 24h period was subtracted from the value of each time point. Mean values across all subjects are presented per period and averaged across all 4 periods.

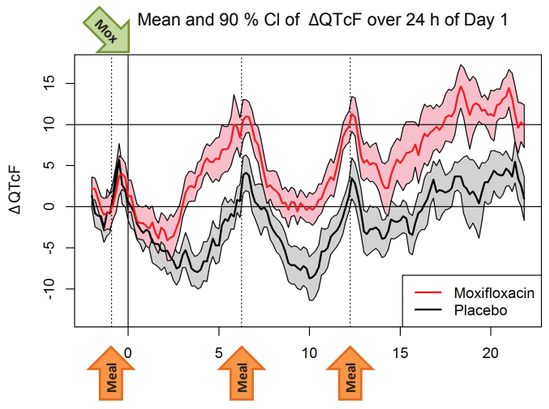

Fig 2: Time course of QTcF and HR on Day 1. For each subject the average over the 24h period was subtracted from the value of each time point. Mean values across all four periods across all subjects are presented by treatment and the two-sided 90% CIs are represented by the shaded areas.

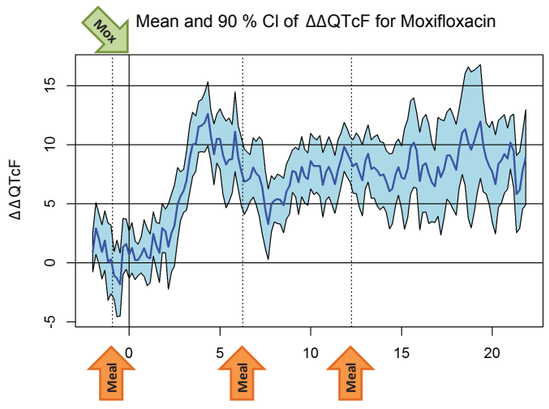

Fig 3: Time course of ΔΔQTcF (change from average baseline and from placebo) and HR on Day 1. Mean values are presented and the 90% CI is represented by the light blue shading.

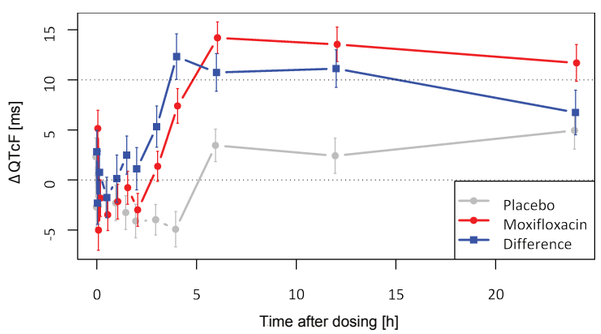

Fig 4: Placebo and moxifloxacin mean change from average baseline (ΔQTcF) and moxifloxacin time matched placebo corrected change from baseline (ΔΔQTcF). The 90% CIs are shown as vertical lines and the threshold of 10 ms is shown as a horizontal dotted line.

Conclusions

- The moxifloxacin profile was consistent with previous studies where moxifloxacin was administered in the fed state, whereby the peak of the QTc effect is delayed if oral moxifloxacin is administered after a meal [4].
- Our baseline results showed a distinct diurnal rhythm, with a significant difference between day and night. The effect of meals on QTcF was seen in the time course plots following placebo administration. This study confirms that the QT interval shortening in response to standardized meals is reproducible and independent of time of day and shows the inverse relation between HR and QTcF as previously reported after food intake [5].
- These Holter results emphasize the importance of activity and feeding effects in defining the diurnal variation in QT-interval as demonstrated by the short-lasting peak in HR values during the 3-4 hours after dose which corresponds to the end of bed rest required for post-dose study assessments.
- A QTcF-prolongation above the threshold of concern was seen with moxifloxacin, when adjusted for meal-and sleep-effects – by subtracting placebo and baseline effects – that persists to the end of the monitoring period, and probably beyond.
- The results presented suggest that the relationship between moxifloxacin concentration and the effect being measured is not a simple direct relationship. This is of relevance to current concentration-effect modelling approaches which presume the absence of hysteresis effects.

References

1. ICH E14 Guideline: (R3) 2015
2. Hong T. Drug Des Devel Ther. 2015;9:1233–1245.
3. Täubel J. Br J Clin Pharmacol. 2017;83(2):339-348
4. Täubel J. Br J Clin Pharmacol. 2014;77(1):170-9.
5. Täubel J. J Clin Pharmacol. 2012;52(10):1558-1565.

RICHMOND Pharmacology
www.richmondpharmacology.com

St George's University of London