The 24 Hour Profile of Moxifloxacin Effect on QTc – A Reflection of Diurnal Variations

J. Täubel[1], P. Foley[1], S. Fernandes[1], G. Ferber[2]

[1]Richmond Pharmacology Ltd, London, United Kingdom; [2]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 PK-QTc analysis points to a linear relationship between the plasma concentration of moxifloxacin and the increase in QTc interval from baseline[2]. Recently moxifloxacin has been used in concentration-effect modelling (CEM), wherein models assumed the absence of hysteresis. However, hysteresis effects have been observed, although the authors attributed them to environmental factors.[3]

This study aims to define the time course of the effect of moxifloxacin on the QT-interval with continuous Holter data in order to better understand the true time-course of the QTc prolongation attributed to moxifloxacin. Reliable methods to verify the absence of hysteresis are essential to allow drawing valid conclusions from CEM to assess QT liability in small studies, yet little is known about QTc effects beyond the intensive PK and ECG sampling typically done up to 12 hours after administration.

Methods

We performed a post-hoc analysis on 12-lead Holter data obtained during a TQT study published by Taubel et al 2017[4]. The data was recorded simultaneously using dual electrodes and the fully automated Holter data was compared with the readings obtained from direct 12 lead standard bedside ECG obtained in the clinic with subsequent cardiologist-adjudication.

ECG data was obtained by 12 lead Holter monitor 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 (Fig 2.). This poster presents the moxifloxacin challenge part of the study only.

Extraction of Holter data was conducted by averaging each three consecutive beats and each value was compared to an average of 22 (about 1 min) adjacent values in order to remove outliers. Values were excluded if the difference between the QTcF value and the average was >5%. Finally, averages over 10 min time segments were calculated and mean time courses presented. The analysis is explained in the legend to Fig 1. The diurnal changes in QTcF are shown in Fig 2.

Results

1. The effect of moxifloxacin exposure is seen after a delay of 4 h after dosing with a point estimate (90% CI) of 7.4 ms (5.7 – 9.1 ms), which is due to the moxifloxacin dose being administered after breakfast leading to a delay in absorption and additionally to a direct reduction of the moxifloxacin effect. That is: the direct effects of the meal partly offsetting the hERG-block, thereby partly compensating the drug effect[5].
2. The QTcF prolonging effect persists to the end of the Holter recordings 24 h after dose administration when QTcF remains prolonged by 11.7 ms (9.9 – 13.5) which is only a few milliseconds less than the peak effect.

Results

Diurnal time course of ΔΔQTcF and the response to Moxifloxacin

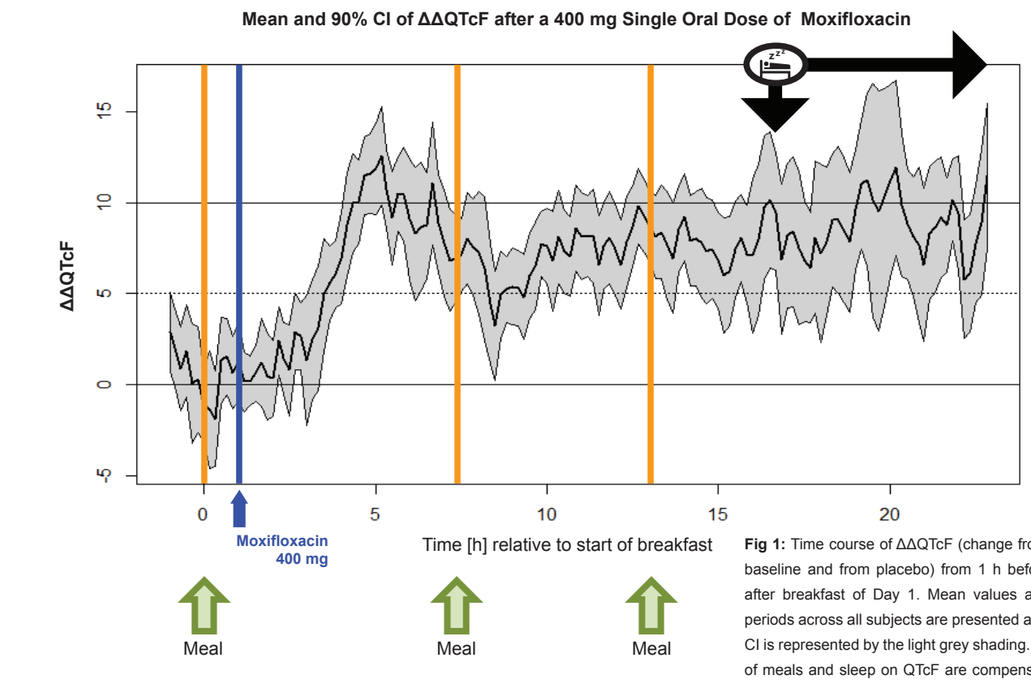

Fig 1: Time course of ΔΔQTcF (change from average baseline and from placebo) from 1 h before to 23 h after breakfast of Day 1. Mean values across all 4 periods across all subjects are presented and the 90% CI is represented by the light grey shading. The effects of meals and sleep on QTcF are compensated for as this effect is removed by subtracting first the baseline data before subtracting the placebo data to calculate the double difference (ΔΔQTcF). Times of moxifloxacin administration and of meals and times of sleep are indicated.

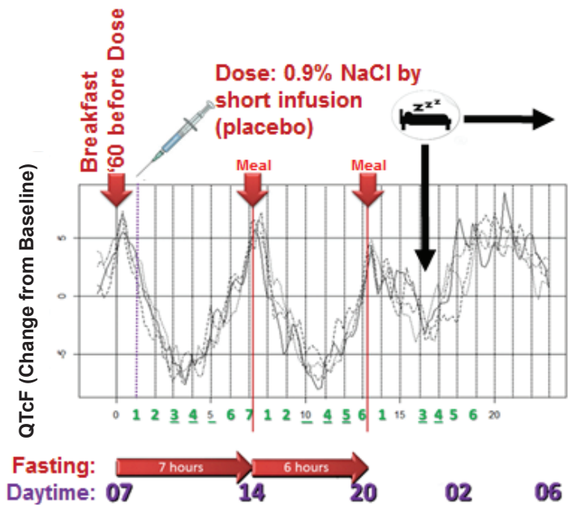

Fig 2. Effect of meals and sleep on QTc: Mean time course

Ingestion of a meal shortens cardiac repolarization times[11] while sleeping lengthens them.[13]

Meals were served as follows: breakfast, 1 hour prior to study drug administration and consumed up to 30 minutes before dosing; lunch, 7 hours post-dose; and dinner, 13 hours post-dose. Breakfast, which is the reference meal in this study, contained 515.7 kcal with an approximated ratio of 23% carbohydrate to 58% fat to 19% protein. Each meal was followed by a reduction of QTcF by approximately 7-13 ms. Sleeping was accompanied by a prolongation of QTcF by approximately 11-12 ms.

Discussion

The plot of continuous QTcF monitoring after a 400 mg dose of moxifloxacin shows that the prolongation of cardiac repolarisation extends well beyond the period in which the plasma exposure would be expected to be effective as moxifloxacin shows a T_{max} of 1.5 h in human plasma[6]. The well-established PK parameters for moxifloxacin (e.g. C_{max} = 2.17 µg/ml/70 kg; T_{max} = 1.0-1.5 h; $T_{½}$ = 9.2 h)[7] indicate that the administered moxifloxacin will have largely disappeared from the systemic circulation. Typical plasma concentrations found 24 hours after 400 mg moxifloxacin administration[12] are 625 µg l^{-1}. This is well documented and the PK values are so well known that the FDA no longer requires the measurement of PK levels in TQT studies as the data is very uniform across them. Thus, our observations indicate that moxifloxacin acts in a non-linear fashion on the repolarizing K^+-conductance, an observation made by other groups[3].

This long-term persistence of the moxifloxacin effect on cardiac repolarization could be the result of irreversible inhibition of the hERG channel function, which is quite different from those substances that only interact briefly and linearly with their plasma concentrations, such as for example amisulpride[4]. Patch-clamp studies have shown that the binding of moxifloxacin to hERG is reversible and use-dependent[8], thus the long-term effect on repolarization may be exerted through another long-term mechanism, such the production of the pharmacologically active moxifloxacin glucuronide metabolite[9] or the inhibition of expression or trafficking of hERG to the cardiomyocyte plasma membrane[10].

Conclusions

- The present report shows a beat-to-beat QTcF analysis validated against the gold-standard 12 lead bedside ECG recordings – adjudicated by well qualified cardiologists experienced in this field. This provides a better understanding of the time-course of the moxifloxacin effect, showing that the effect of the drug lasts beyond 24 hours when ΔΔQTcF is still raised well above the threshold of concern and beyond what could be expected from the corresponding plasma concentration.
- This is a finding relevant to the assessment of QT-prolongation as all currently used concentration-effect modelling approaches assume that there are no hysteresis effects. The relevance of hysteresis is still under discussion.
- Tools that differentiate the CE versus time behaviour would aid validation of the use of CEM models in new molecules. Therefore intensive PK sampling combined with simultaneous ECG should be extended beyond the 3 – 5 time half-life to allow a better quantification of hysteresis should it occur.

References

1. ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions & Answers (R3) 2015
2. Florian JA et al, J Clin Pharmacol 2011;51(8):1152-62
3. Kumagai Y, et al, PlosOne. 2015;10(10): e0139873
4. Taubel J et al, Br J Clin Pharmacol. 2017;83(2):339-348
5. Taubel J et al, CPT Pharmacometrics Syst Pharmacol. 2017;6(5):283
6. Barman Balfour JA, Wiseman LR. Drugs. 1999;57(3): 363-373.
7. Lubasch A, et al. Antimicrob Agents Chemother. 2000;44(10): 2600-2603; FDA (2002) AVELOX (moxifloxacin hydrochloride) Tablets, https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21085s12lbl.pdf
8. Alexandrou et al, B J Pharmacol 2006:147(8): 905-16
9. Johannesen L Clin Pharmacol Ther. 2016;99(2):214-23
10. Nogawa H et al, Eur J Pharmacol, 2013;720: 29-37; Nogawa H & Kawai T, Eur J Pharmacol, 2014;741: 336-9
11. Taubel J & Ferber G, J Electrocardiol. 2015;48(2):274-5.
12. Zvada SP , et al. Antimicrob Agents Chemother. 2014;58(1):503-10
13. Browne KF et al, Am J Cardiol. 1983;52(1):55-9.