The cardiovascular effects of a meal: assessment of the effects on J-T_{peak} and T_{peak}-T_{end} intervals

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Introduction

A meal is associated with sympathetic activation of the cardiovascular system and food ingestion is correlated with an increase in heart rate an increase in cardiac stroke volume and QTc interval shortening for up to 7 hours [1]. Given the complexity of the system, one or several of many mechanisms could explain this observation. The shortening of the QTc interval was correlated with a rise of C-peptide following food ingestion, but the mechanisms by which C-peptide may be involved in the modulation of cardiac repolarization are still unknown.

This study aimed to further investigate the shortening of action potential duration caused by a meal intake by measuring the QRS, J-T_{peak} and T_{peak}–T_{end} intervals in search of further clues to better understand the underlying mechanisms.

Methods

Study design: The retrospective analysis reported here was based on the data from an already published TQT study where 400 mg moxifloxacin was administered orally as a positive control [2, 3]. Data from the following treatment sequences were used: a carbohydrate rich 'continental' breakfast, moxifloxacin 400 mg, moxifloxacin 400 mg administered with a carbohydrate rich 'continental' breakfast and placebo. The study was designed as a single centre, randomized, placebo- and positive-controlled, crossover study. Breakfast was given 30 min before dose and the next meal was given 7 hours after dose. The study enrolled 32 healthy non-smoking, Caucasian and Japanese male and female subjects.

ECG data processing: Data was processed by the Department of Health Science and Technology of the Faculty of Medicine, University of Aalborg (Denmark) using the commercially available GE Healthcare Marquette 12SL ECG analysis program and the US Food and Drug Administration 510(k)-cleared GE research package QT GuardPlus, which uses validated algorithms for measurement.

Statistical analysis: The baseline-corrected variables (ΔQRS, Δ J-T_{peak}cS and ΔT_{peak}-T_{end}) were obtained by subtracting the pre-dose value of QRS, the HR-corrected J-T_{peak} and T_{peak}-T_{end}, calculated by time point and subject and period, from the post-dose corrected value, matched by subject, and timepoint and period.

The HR- and baseline-corrected outcome variables were used (ΔQRScS, ΔJ-T_{peak}-cS and ΔT_{peak}-T_{end}-cS – cS: correction-Specific) for the main statistical analysis.

The time-point effect analysis involved one mixed model for each variable with the interaction between treatment and timepoint as fixed effect, scaled baseline value as covariate and varying baseline for each subject as random effect.

Discussion and Conclusions

- The main effect of a meal on cardiac repolarisation seen in this study was a shortening of J-Tpeak. A smaller effect was seen in the QRS and T_{peak}-T_{end} intervals mainly during the first hour.
- This effect corresponds to an effect on Phase 2 of the cardiac myocyte action potential i.e an influx of Ca^{2+}. These findings suggest that the mechanism by which food affect J-T_{peak} may potentially be associated with the signaling pathways of calcium cycling.
- Previous work suggest that C-peptide may elicit changes in cardiac repolarization through a potential interaction with Ca^{2+} cycling in the cardiac myocyte, as one possible explanation for QTc shortening after a meal [4, 5].
- Moxifloxacin equally prolonged J-T_{peak} and T_{peak}-T_{end} and food reduced the effect of moxifloxacin on the QTc, primarily during the J-T_{peak} interval with little or no effect on the T_{peak}-T_{end} interval.
- Food exerts a particular effect on early repolarization and a decrease in shortening of the J-T_{peak} interval was seen with moxifloxacin in the fed state even when the differences in plasma concentrations between fed and fasted are taken into account.

Results

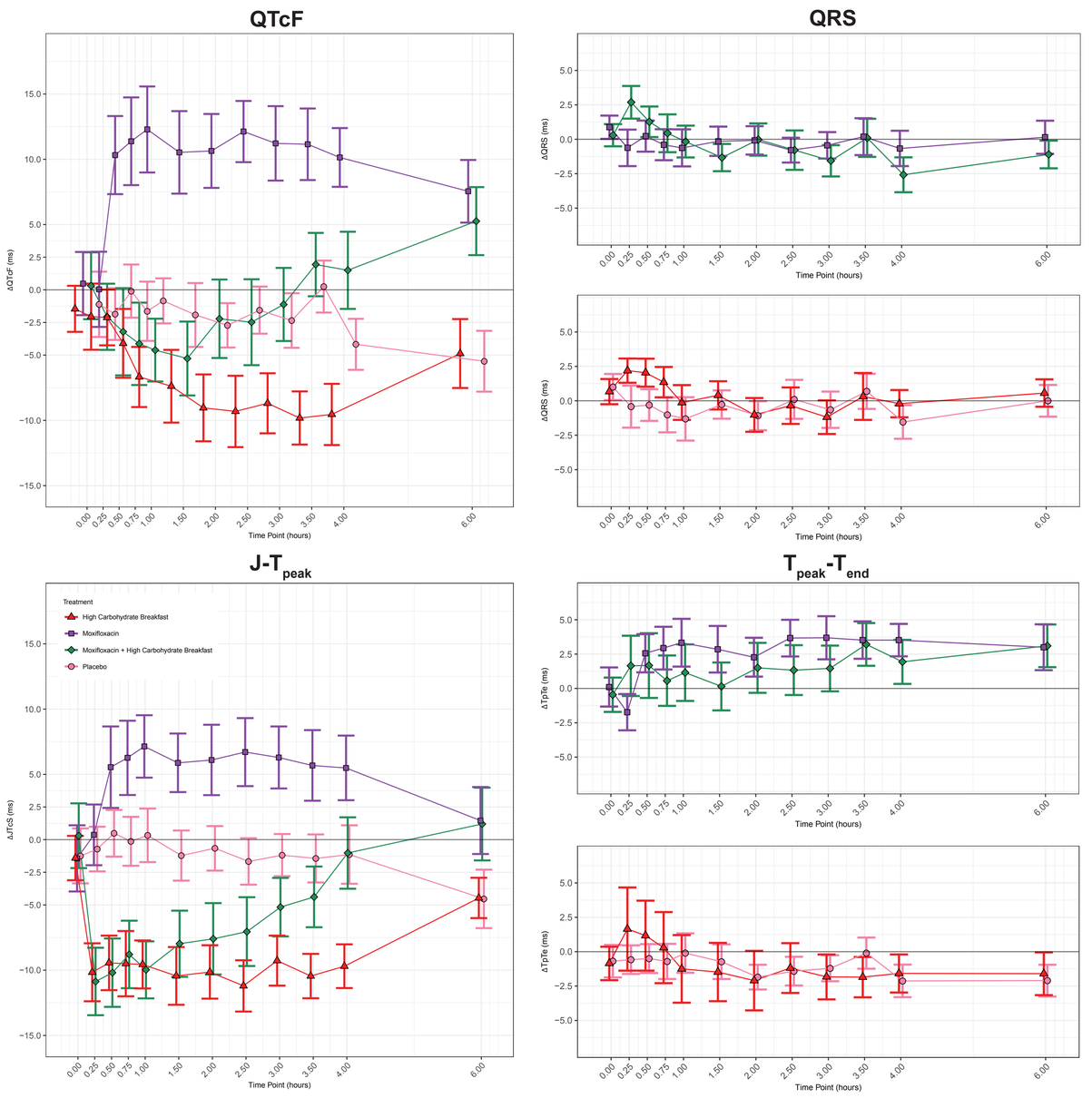

Fig 1: Time-course of change from time-matched baseline: ΔQRS-cS (A), ΔJ-T_{peak}-cS (B) and ΔT_{peak}-T_{end}-cS (C) by treatment group. The two-sided 90% confidence intervals are shown as vertical lines.

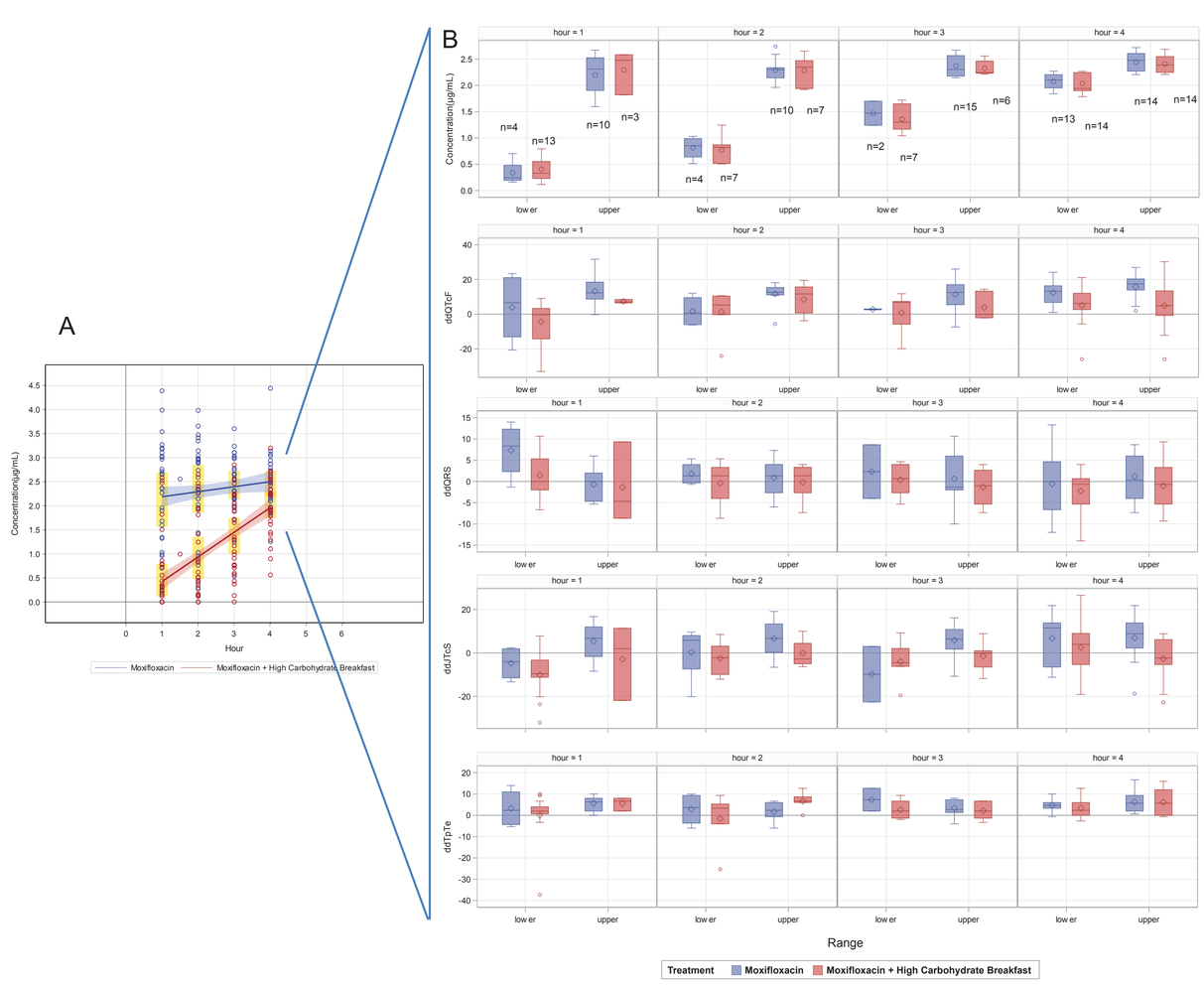

Fig 2: A) Individual plasma concentrations of 400 mg moxifloxacin in fasted and fed state. The individual moxifloxacin concentrations, plotted by feeding status showing the delay in absorption when moxifloxacin is taken after a carbohydrate rich breakfast. B) At 1, 2 , 3 and 4 hours the plasma concentrations were restricted to limited ranges at the upper and lower ends. This restriction showed similar concentrations for fasted moxifloxacin and moxifloxacin + breakfast in each range. Fasted placebo was subtracted from the moxifloxacin fasted and moxifloxacin fed treatments showing a decrease in QTcF and J-T_{peak} when moxifloxacin is given with food. This supports the findings that food has an effect on early repolarization.

References

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