ASSESSMENT OF C-PEPTIDE EFFECTS ON CARDIAC ION CHANNEL CURRENTS

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Introduction

The effect of food on QTc has been reported in different studies [1-3]. A standardized meal would be expected to induce a decrease in QTcF of 6-8 ms after food intake correlated to an increase in heart rate [4]. The cardiac shortening of action potential duration (APD) was correlated with a rise of C-peptide following food ingestion. However, the mechanisms by which C-peptide apparently modulates cardiac repolarization are still unknown. This study aimed to better understand which ion channels may be involved in the meal response and better characterize the ECG signature and impact of food on T-wave morphology. Potential relationships between the ECG subintervals and C-peptide concentrations were further explored.

Methods

Study design: The retrospective analysis reported here was based on the data from an already published TQT study where moxifloxacin was administered as a positive control [4, 5]. Data from the following treatment sequences were used: a carbohydrate-rich ‘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. 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 125E 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 outcome variables were obtained by subtracting the pre-dose value of the corrected QRS-JT-Tpeak-Tend-cS from the post-dose corrected value, matched by subject and timepoint. The HR- and baseline-corrected outcome variables were used (∆QRST, ∆JTcS, ∆Tpeak-Tend-cS, ∆C-peptide concentrations were further explored.

Results

QRSt
• QRS increased from baseline between 15 minutes and 2 hours after time zero in the treatment groups that received a high carbohydrate breakfast with and without moxifloxacin (Fig 1). Moxifloxacin alone showed no change and a very small short-lived prolongation 45-60 minutes after dose (time zero).
• No significant changes of QRS between moxifloxacin fasted and fed were observed (Fig 2).

Discussion

• 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 Tpeak-Tend intervals.
• The results of this study showed that the QTc shortening occurs mainly during Phase 2 of the cardiac action potential and aligns well with our understanding of physiology whereby an increase in stroke volume (SV), as observed after a meal, is associated with changes in Ca$^{2+}$ cycling in the cytoplasm.
• C-peptide was shown to induce intracellular Ca$^{2+}$ increases in human renal tubular cells [6] indicating that the same occurrence could be observable in cardiomyocytes.
• C-peptide was also shown to stimulate the activity of the Ca$^{2+}$-sensitive eNOS by increasing the influx of Ca$^{2+}$ into endothelial cells [7].
• The concurrence of C-peptide concentration with QTc shortening suggests that C-peptide may play a role in the Ca$^{2+}$ cycling in the cardiac myocyte.
• As C-peptide receptors remain a mystery, further investigations are required to understand the role of C-peptide and determine the underlying mechanisms of the direct impact on cardiac repolarization during the postprandial period.
• Moxifloxacin equally prolonged J-Tpeak and Tpeak-Tend. As reported previously, the ECG signature of moxifloxacin was consistent with the signature of other pure HERG potassium channel block [8].
• Food reduced the effect of moxifloxacin on the QTc, primarily during the J-Tpeak interval and modestly in the Tpeak-Tend interval. Yet it was not possible to assess the pro-arrhythmic effects, i.e whether food would ameliorate the propensity of moxifloxacin to induce Torsade de Pointes.

References