

ALTERNATIVE METHODS FOR THE CONFIRMATION OF ASSAY SENSITIVITY IN THOROUGH QT STUDIES

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Introduction

Moxifloxacin is most commonly used as a positive control to confirm assay sensitivity as mandated by ICH E14 guidelines^{1, 2, 3}. Moxifloxacin is well established and well published in producing average QT prolongation (QTcF) of usually 10 msec or greater^{4, 5} following a 400 mg single dose. This larger than originally anticipated effect is addressed in the ICH E14 implementation group Questions and Answers document in relation to assessing the adequacy of positive controls in TQT studies⁶. This led to the requirement that at least one of the lower bounds of the confidence intervals must be greater than 5 msec⁴.

Therefore, an alternative method of confirming assay sensitivity which is able to detect small changes around the regulatory threshold has been proposed⁵. Levofloxacin, has been shown to lead to smaller increases in QTc thus has the potential to provide a more rigorous evaluation of assay sensitivity by leading to a mean change in QTc of only around 5 msec⁷.

Furthermore, a non-pharmacological approach may be desirable in studies where the use of moxifloxacin is undesirable. The use of postural changes has been proposed⁸ but this method has been found to be impractical and ECG measurements may be affected by hysteresis i.e. the period of QT to RR adaptation after a change in heart rate during which accurate measurements of the QTc interval is impossible⁹. More recently a study has demonstrated that food may cause a prolonged and pronounced change in QTc which may warrant its use as a non pharmacological method of confirming assay sensitivity.

Aims

In this study, the effect of different meal compositions (carbohydrate rich versus standard FDA breakfast) on the QT/QTc interval under the conditions of a TQT study was investigated. Assay sensitivity was confirmed by the use of a positive control (400 mg moxifloxacin).

Methods

This presentation used data obtained during a TQT study that was compliant with International Conference on Harmonization (ICH) E14 guideline. The data presented originates from an open-label, randomised, placebo-controlled, crossover study that evaluated the effect of different food content on the QT/QTc interval of the ECG using a single 400 mg dose of moxifloxacin as a positive control in non-elderly healthy male and female, Caucasian and Japanese volunteers.

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.

Food content

Scott et al (2002) demonstrated an increase in the heart rate of 10bpm in some healthy subjects following ingestion of a carbohydrate meal. There was significant correlation between the resultant hyperinsulinaemia and an increase in skeletal muscle blood flow, and sympathetic activity, with a reduction in vascular resistance. If postprandial insulinaemia is a significant influence on the QT interval, then carbohydrate rich meals would be expected to show greater effect.

Therefore, to explore this on two separate days of the study subjects were given one of two different types of breakfast:

- A high carbohydrate content breakfast, (>70% carbohydrate)
- A reduced calorie FDA standard breakfast, (low carbohydrate content).

Subjects randomised to a high carbohydrate breakfast or a calorie reduced FDA standard breakfast, received the breakfast 30 minutes prior to anticipated 'dosing time' and consumed 10 minutes before anticipated 'dosing'. The carbohydrate content of the breakfasts were as follows:

High carbohydrate = 134g (536kcal) – 81% of total content
Carbohydrate reduced = 30g (119kcal) - 29% of total content.

The sensitivity of the study was confirmed by moxifloxacin 400 mg (single dose) showing a QTcF prolongation of 14.5 msec.

Data Analysis & Statistical Methods

The digital ECG recordings were transmitted electronically to the ECG core laboratory for computer based, manually verified, digital calliper measurement of conduction intervals (RR, PR, QRS and QT) using a threshold method assessing a computer derived global beat using the MUSE Interval Editor (GE Healthcare). All ECGs for a given subject were read by the same person and in blinded fashion.

Safety Assessment

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

Results

Effect of high carbohydrate content breakfast on QTc

Mean QTcF was shortened in subjects receiving high carbohydrate breakfast (>70%) compared with placebo. The greatest effect was observed at 3 hours post ingestion (Figure 1).

- mean change in QTcF [90%CI]: -7.6 [-10.6 , -4.6] msec

Effect of reduced calorie FDA standard content breakfast on QTc

Mean QTcF was shortened in subjects receiving reduced calorie FDA standard breakfast compared with placebo. The greatest effect was observed at 2.5 hours post ingestion (Figure 1).

- mean change in QTcF [90%CI]: -6.5 [-9.4 , -3.5] msec

Effect of Moxifloxacin 400 mg on QTc

Mean QTcF was prolonged at 3.5 hours post-dose in subjects receiving moxifloxacin 400 mg compared with placebo.

- mean change in QTcF [90%CI]: 14.5 [12.11-16.9] msec

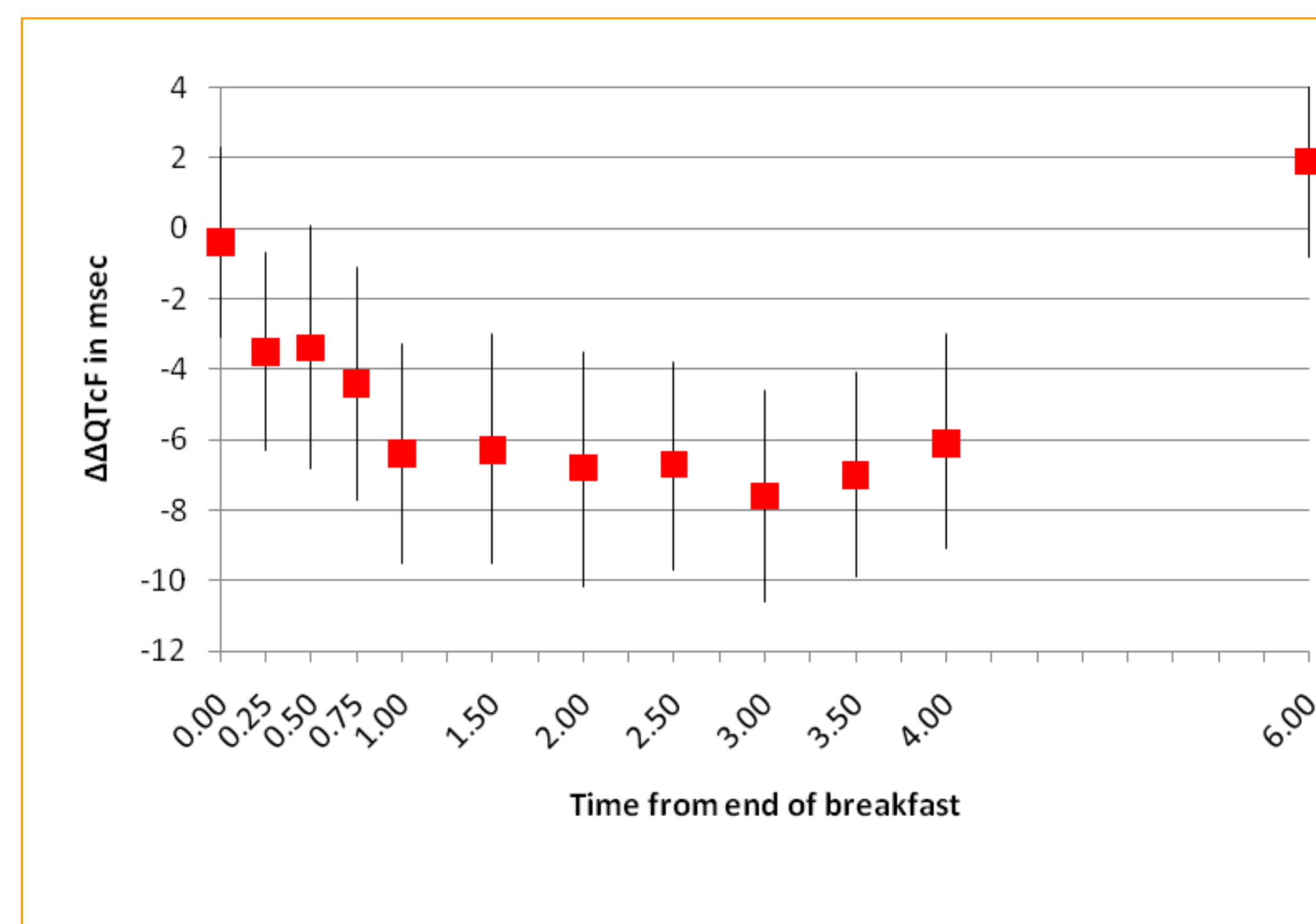


Figure 1 Effect of a carbohydrate rich breakfast on ΔΔQTcF in 24 Japanese and Caucasian male and female healthy subjects

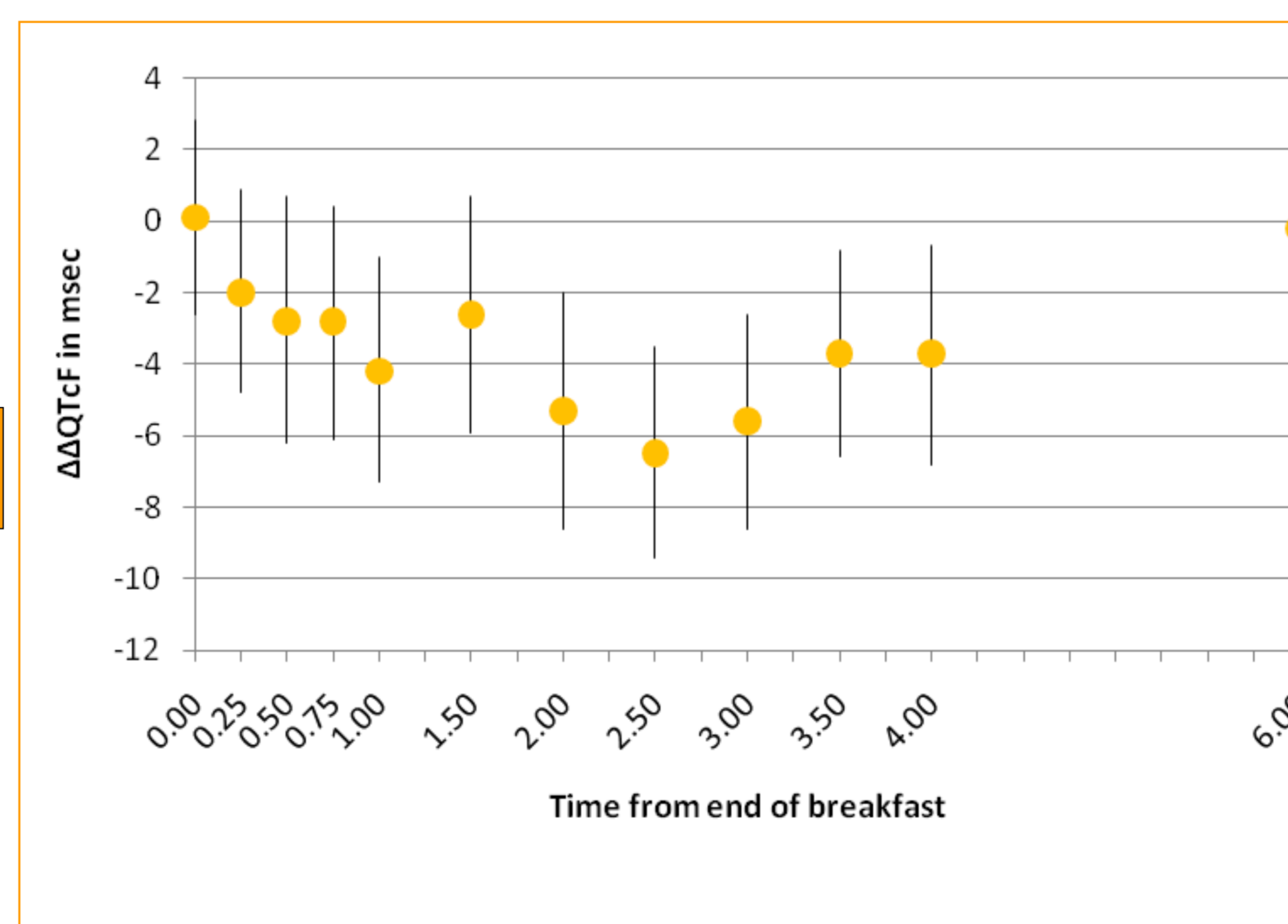


Figure 2 Effect of a carbohydrate reduced breakfast on ΔΔQTcF in 24 Japanese and Caucasian male and female healthy subjects

Discussion

Meals of high carbohydrate content have been associated with transient endogenous physiological insulinaemia¹⁰. If postprandial insulinaemia plays a significant role in the observed effects of food on ECG, then meals with high levels of carbohydrates would be expected to show a greater effect.

This is demonstrated in this study with the high carbohydrate (>80%) meal producing a QTcF shortening of 7.6 msec and the calorie reduced FDA meal (<30%) producing a QTcF shortening of 6.5 msec. Although not statistically significant (the CI for the two breakfasts overlap) the findings show a trend of greater QTcF shortening with higher carbohydrate content. This finding is similar to that reported with a carbohydrate meal content of 68% which demonstrated a QTcF shortening of 8.2 msec (95% CI: 6-10 msec)¹¹ and with other studies using high carbohydrate content meals^{12, 13}.

The changes observed in QT and QTc interval following food appears to be more pronounced with high carbohydrate content and is fully reproducible compared with an earlier study demonstrating the same effect¹¹. These findings fulfil the requirements of a non-pharmacological method of assay sensitivity confirmation. The food effect observed is much closer to the ICH E14 requirements of 5 msec compared with moxifloxacin¹¹. Even though the change is negative (QTcF shortening of 7.6 msec) the direction of the effect is not important when considering that the assay control is used to confirm that the study is capable of detecting small changes.

A standardised food arm could be used as an alternative method to demonstrate assay sensitivity in a wide range of studies providing an assurance that these trials would be sufficiently sensitive of detecting an effect on the QTc interval of around 5 to 10 msec.

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