

Meta-analysis of the effect of a meal on QTcF

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Introduction

Meal intake leads to a significant and prolonged increase in cardiac output to supply the splanchnic vasculature [1]. 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 seven hours. In thorough QT studies, the consistent shortening effect on the QT interval caused by food intake can be used as a non-pharmacological positive control [2].

Methods

In this meta-analysis, 12 separate thorough QT studies conducted at Richmond Pharmacology Ltd, London, UK were analysed alongside one another to observe the consistency of the effect of a meal on the QTc interval, and to observe any trends associated with sex. Four of the studies used breakfast to observe an effect of a meal, four used lunch, and four studies observed QTc shortening in fasted individuals. For breakfast and lunch, post-prandial data was compared with pre-prandial, for fasted, post-dose was compared with pre-dose.

Primary analysis was based on a set of ANOVA models with change from pre-prandial QTcF as the dependent variable and study and sex as independent variable. To compare the effects of breakfast, lunch or fasting, weighted means of the four studies in each set were used.

Results

Weighted mean across studies

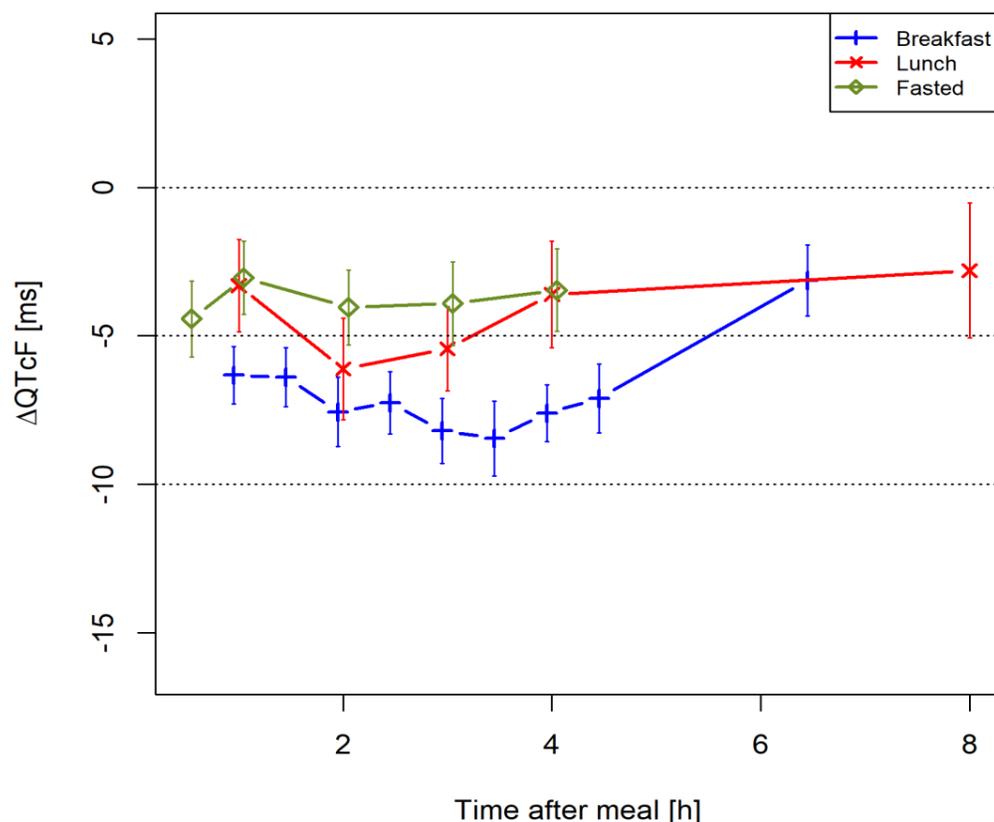


Figure 1. Weighted means for all studies, showing post-prandial shortening of QTcF.

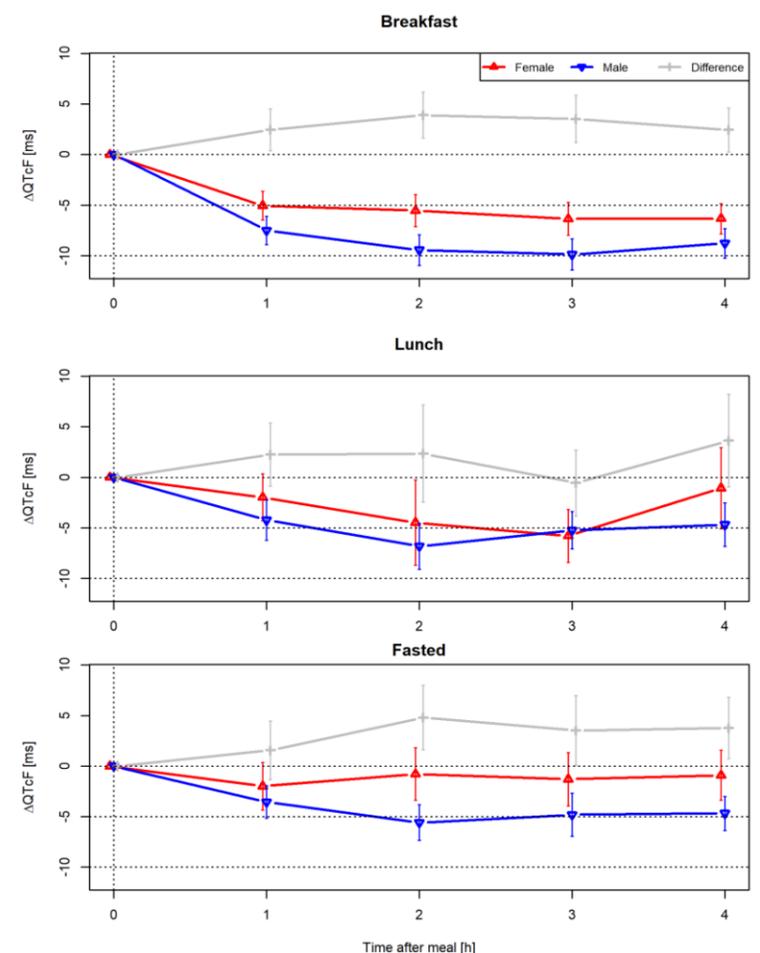


Figure 2. Weighted means presented for each meal, stratified by sex

Conclusions

- Data showed a consistent shortening effect caused by the intake of food during breakfast and lunch, further confirming that the food effect is a robust method of confirming assay sensitivity in thorough QT studies [2].
- The mean shortening effect for breakfast was maximal at 3.5 hours after food intake, with a QTc shortening of 8.5 ms. The shortening effect after lunch was maximal at 2 hours after food intake at 5.6 ms. Interestingly, a shortening effect of 5.8 ms was also observed in the fasted group after 3.5 hours. Breakfast appears to have a larger shortening effect than lunch.
- Male volunteers experience larger shortening than females during breakfast and fasting, but not to the same extent following lunch.
- We hypothesise that this is due to changes in autonomic tone after the studies were in progress. Further modelling is ongoing to highlight the role of the food effect and the effect of autonomic tone in QTcF shortening in QTcF studies.
- Further work is planned to investigate the relationship of other demographic parameters, and to investigate further the different effects of breakfast and lunch.

References

[1] Taubel et Al. J Clin Pharmacol 2019;59(6):799-810

[2] Ferber et Al. J Clin Pharmacol. 2018;58(1):81-88