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

Jorg Taubel1, Asif Naseem1, Juleen Gayed1, Georg Ferber1 and A. John Camm2
1Richmond Pharmacology Ltd., St George’s University of London, Cranmer Terrace, London, United Kingdom.
2Department of Cardiological Sciences, St George’s University of London, Cranmer Terrace, London, United Kingdom.

Introduction

Moxifloxacin is most commonly used as a positive control to confirm assay sensitivity as mandated by ICH E14 guidelines1-3. Moxifloxacin is well established and well published in producing average QT prolongation (QTcF) of usually 10 msec or greater6-8 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 studies4. This lead 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 msec.

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.

Results

Food content

Scott et al (2002) demonstrated an increase in the heart rate of 105pm 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 insulinemia 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
- Calorie 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 QT/QTc interval.

The changes observed in QT and QTc interval following food intake are due to transient hyperglycaemia and resultant hyperinsulinaemia 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.

Effect of Carbohydrate Rich Breakfast on QTcF

Mean QTcF was prolonged at 3.5 hours post-dose in subjects receiving moxifloxacin 400 mg 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 Carbohydrate Reduced Breakfast on QTcF

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

Discussion

Meals of high carbohydrate content have been associated with transient endogenous physiological insulinemia8. If postprandial insulinemia 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)10 and with other studies using high carbohydrate content meals11, 12.

The changes observed in QT and QTc interval following food intake are due to transient hyperglycaemia and resultant hyperinsulinaemia 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.

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.

References

5. Jorg Taubel1, Asif Naseem1, Juleen Gayed1, Georg Ferber1 and A. John Camm2. ALTERNATIVE METHODS FOR THE CONFIRMATION OF ASSAY SENSITIVITY IN THOROUGH QT STUDIES. Richmond Pharmacology Ltd., St George’s University of London, Cranmer Terrace, London, United Kingdom.