Insulin at normal physiological levels does not prolong QT$_c$ interval in thorough QT studies performed in healthy volunteers

Jorg Taubel,[1] Ulrike Lorch,[1] Georg Ferber,[1] Jatinder Singh,[1] Velislav N. Batchvarov,[2] Irina Savelieva[2] & A. John Camm[2]

[1]Richmond Pharmacology Ltd, St George's University of London, London, UK, [2]Cardiovascular Sciences Research Centre, Division of Clinical Sciences, St George's University of London, London, UK

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- A meal, in particular if rich in carbohydrates alters the QT/RR relationship. This is of interest since this shows that normal physiological changes can alter QT$_c$ significantly.
- The underlying effects of QT$_c$ shortening after a meal are currently unknown. A meal leads to the release of C-peptide and insulin in equimolar amounts.
- QT$_c$ shortening after administration of C-peptide has been described by other authors and one study has reported that insulin prolongs the QT$_c$.

WHAT THIS STUDY ADDS

- This study investigates the effect of insulin on the QT interval under the rigorous conditions of a thorough QT (TQT) study using a single dose of 400 mg moxifloxacin as a positive control.
- Insulin concentrations during the euglycaemic clamp were raised to constant concentrations of about 45 µIU ml^{-1} during which endogenous C-peptide release was successfully suppressed.
- During the euglycaemic clamp, no significant change was observed in QT$_c$F. The greatest effect observed was a QT$_c$F shortening of 2.6 ms (95% CI −5.3, 0.2), 1.5 h into the clamp. The observation that insulin does not influence QT$_c$F was confirmed by a concentration–response analysis which revealed that QT$_c$ shortening was due to C-peptide and that glucose counteracted this thereby partially offsetting the effect of C-peptide leading to a net QT$_c$F decrease.

AIMS

Food is known to shorten the QT$_c$ (QT$_c$I and QT$_c$F) interval and has been proposed as a non-pharmacological method of confirming assay sensitivity in thorough QT (TQT) studies and early phase studies in medicines research. Intake of food leads to a rise in insulin levels together with the release of C-peptide in equimolar amounts. However, it has been reported that euglycaemic hyperinsulinemia can prolong the QT$_c$ interval, whilst C-peptide has been reported to shorten the QT$_c$ interval. Currently there is limited information on the effects of insulin and C-peptide on the electrocardiogram (ECG). This study was performed to assess the effect of insulin, glucose and C-peptide on the QT$_c$ interval under the rigorous conditions of a TQT study.

METHODS

Thirty-two healthy male and female, Caucasian and Japanese subjects were randomized to receive six treatments: (1) placebo, (2) insulin euglycaemic clamp, (3) carbohydrate rich 'continental' breakfast, (4) calorie reduced 'American' FDA breakfast, (5) moxifloxacin without food, and (6) moxifloxacin with food. Measurements of ECG intervals were performed automatically with subsequent adjudication in accordance with the ICH E14 guideline and relevant amendments.

RESULTS

No effect was observed on QT$_c$F during the insulin euglycaemic clamp period (maximal shortening of QT$_c$F by 2.6 ms, not significant). Following ingestion of a carbohydrate rich 'continental' breakfast or a calorie reduced 'American' FDA standard breakfast, a rapid increase in insulin and C-peptide concentrations were observed. Insulin concentrations showed a peak response after the 'continental' breakfast observed at the first measurement time point (0.25 h) followed by a rapid decline. Insulin concentrations observed with the 'American' breakfast were approximately half of those seen with the 'continental' breakfast and showed a similar pattern. C-peptide concentrations showed a peak response at the first measurement time point (0.25 h) with a steady return to baseline at the 6 h time point. The response to the 'continental' breakfast was approximately double that of the 'American' FDA breakfast. A rapid onset of the effect on QT$_c$F was observed with the 'continental' breakfast with shortening by >5 ms in the time interval from 1 to 4 h. After the 'American' FDA breakfast, a similar but smaller effect was seen.

CONCLUSIONS

The findings of this study demonstrate that there was no change in QT$_c$ during the euglycaemic clamp. Given that insulin was raised to physiological concentrations comparable with those seen after a meal, whilst the release of C-peptide was suppressed, insulin appears to have no effect on the QT$_c$ interval in either direction. The results suggest a relationship exists between the shortening of QT$_c$ and C-peptide concentrations and indicate that glucose may have a QT$_c$ prolonging effect, which will require further research.