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

1. Jorg Taubel1,*
2. Ulrike Lorch1
3. Georg Ferber1
4. Jatinder Singh1
5. Velislav N Batchvarov2
6. Irina Savelieva2
7. A. John Camm2

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Author Information

1 Richmond Pharmacology Ltd., St George's University of London, London, United Kingdom

2 Cardiovascular Sciences Research Centre, Division of Clinical Sciences, St George's University of London, London, United Kingdom

*Correspondence
Dr Jorg Taubel, Richmond Pharmacology Ltd, St George's University of London, Cranmer Terrace, Tooting, London, SW17 0RE, UK.
E-mail: j.taubel@richmondpharmacology.com

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Aims

Food is known to shorten the QTc (QTcI and QTcF) 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 QTc interval, whilst C-peptide has been reported to shorten the QTc 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 QTc interval under the rigorous conditions of a TQT study.

Methods

32 healthy male and female, Caucasian and Japanese subjects were randomised 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 QTcF during the insulin euglycaemic clamp period (maximal shortening of QTcF 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 levels showed a peak response after the ‘continental’ breakfast observed at the first measurement time point (0.25 hours) followed by a rapid decline. Insulin levels observed with the ‘American’ breakfast were approximately half of those seen with the ‘continental’ breakfast and showed a similar pattern. C-peptide levels showed a peak response at the first measurement time point (0.25 hours) with a steady return to baseline at the 6 hour time point. The response to the ‘continental’ breakfast was approximately double that of the ‘American’ FDA breakfast. A rapid onset of the effect on QTcF was observed under ‘continental’ breakfast with shortening by > 5 ms in the time interval from 1 to 4 hour. Under the ‘American’ FDA breakfast, a similar but smaller effect was seen.

Conclusions

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