LATE CHANGES AFTER A EUGLYCAEMIC INSULIN CLAMP CAN LEAD TO SIGNIFICANT INCREASES IN QTcF IN HEALTHY SUBJECTS

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Introduction

In 2000 Gastaldelli et al. described a euglycaemic hyperinsulinaemic clamp study in healthy volunteers concluding that insulin prolongs the QTc interval. We have since shown1,2 that using state of the art equipment, ECG measurements and PK-PD analysis in connection with an appropriate heart rate correction3, there is no direct effect of insulin on QTc.

However, an unexpected late increase in aΔQTc was noticed, occurring one hour after the end of the euglycaemic hyperinsulinaemic clamp experiment. The maximum QTcF prolongation was 8.7ms (90% C.I. 6.5, 10.9) at the six hour time point, i.e. 4 hours after the end of the clamp experiment and at a time where insulin levels had returned to normal baseline values. This paper attempts to put this finding into a clinical perspective.

Aims

One aim of the present TQT study (NCT01642448) was to show that insulin does not prolong QTc during a hyperinsulinaemic euglycaemic clamp experiment and to correlate the plasma concentrations of insulin, glucose and c-peptide to the observed changes in QTcF. Assay sensitivity was to be confirmed by the use of 400mg mofloxacin as a positive control.

Methods

32 healthy Caucasian & Japanese subjects were randomised to receive the following treatments over two periods:

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Period 2</th>
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<tbody>
<tr>
<td>Placebo</td>
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<tr>
<td>Insulin</td>
<td>Insulin</td>
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<tr>
<td>ECG</td>
<td>ECG</td>
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<tr>
<td>10 kg</td>
<td>10 kg</td>
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<td>1 h</td>
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The clamp was run over two hours during which insulin was infused at a constant rate following a loading dose. The glucose infusion was continued until 2.5 hours, i.e. 30 minutes longer. Measurements of QT intervals were performed automatically with subsequent manual adjudication in accordance with ICH E14. Frederica’s formula was used to calculate QTc.

Results

Insulin Clamp Dose Calculations:

For example, if a volunteer weighs 65kg, with a height of 1.74m, the Body Surface Area (Mosteller formula) is calculated as:

\[ \text{BSA} = \left( \frac{\text{Weight (cm) \times Weight (kg)}}{360}\right)^{0.5} \]

\[ = \left( \frac{174 \times 65}{360}\right)^{0.5} = 1.77 \text{ m}^2 \]

The priming insulin infusion rate for 0-2 minutes was calculated as:

\[ 120.6 \text{min/BSA min} \times 1.77^2 = 213.5 \text{mU/min} \]

The maintenance insulin infusion rate was calculated as:

\[ 40 \text{mU/min} \times 1.77^2 = 70.8 \text{mU/min} \]

The total insulin given over 2 hours was calculated as:

\[ \left(2 \times (213.5 + 169.4 + 134.2 + 106.8 + 84.4)\right) + (110 \times 70.8) = 9.2 \text{U} \]

Panel A shows insulin, c-peptide and glucose levels during the 0-2 hour hyperinsulinaemic euglycaemic clamp as well as the 4 hour period (0-6 hours) following the clamp. All values are below the fasting baseline values therefore offering no explanation for the late QTc changes seen from the 3.5 hour time point until the end of the observation period at 6 hours.

Panel B shows the average baseline and placebo corrected change in QTc (aΔQTc) which remains unchanged by the increase in insulin levels during the first two hours and until the 3.5 hour time point, i.e. until 1.5 hours after the end of the clamp. However, from the 3.5 hour time point until the end of the observation period at 6 hours a steep rise in QTcF has occurred. The maximum QTcF prolongation was 8.7ms (90% C.I. 6.5, 10.9) observed at the last measurement time point at 6 hours.

For the data presented in Panel B it was not feasible to show that QTcF was rising further beyond the 6 hour time point or whether a peak had been reached. Therefore a post hoc analysis was carried out, utilising 12-lead Holter recordings which were taken simultaneously to the 12-lead bedside ECG recordings as a backup for supplementary analysis of this kind.

Panel C shows the baseline corrected change in QTcF without placebo correction (ΔΔQTc) using matching baseline ECG data rather than the average baseline correction method. Additional Holter data is depicted by green dots in Panel C in 15 minute intervals between 4 and 6 hours derived from the post hoc analysis of the 12-lead Holter recordings. This shows that a peak of QTcF prolongation has been reached at the five hour time point. There is some fluctuation between 4 to 5 hours, largely due to individuals showing larger swings at different time points. However, the effect appears fairly stable throughout the observation period as demonstrated by a flat linear regression slope for that period.

This supplementary analysis work in progress as the data readout can further be improved by analysing more data.

A major shortcoming in further evaluating these unanticipated changes is the lack blood samples of corresponding to the additional ECG time points elicited from Holter. No potassium samples were taken for this period.

Discussion

To the best of our knowledge this is the first report of QTc prolongation more than 2 hours after the discontinuation of a euglycaemic clamp. Maximum QTcF prolongation was 8.7ms (90% C.I. 6.5, 10.9) at the six hour time point, i.e. 4 hours after the end of the clamp; the upper bound exceeding that defined in ICH E14 and may represent a potential risk to patients. We found no correlation between QTcF, glucose, c-peptide and insulin levels explaining this change.

Clinically insulin glucose infusions are used to lower serum potassium levels in severe hyperkalaemia as it shifts potassium into cells. In the UK usually 10 IU are given with a 50-100ml 25-50% glucose solution over 15-30 minutes. The effect is expected to last for about one hour. During our clamp study we delivered about 9IU over 120 minutes. However, insulin has a short half life and in our study plasma insulin levels had returned to normal baseline values within one hour of the infusion end. Therefore QTcF values started to rise at a time when insulin had returned to baseline.

Potassium is predominantly an intracellular cation; therefore, serum potassium levels can be a very poor indicator of total body stores or concentrations around cardiomyocytes; as a consequence they were not measured in this trial. It is perceivable that our observation represents a change in cardiac repolarisation subsequent to an outward “rebond” shift of potassium from the intracellular to the extracellular space.

Several factors regulate the distribution of potassium between the intracellular and extracellular space: Regulatory hormones: (1) Insulin enhances, (2) glucagon impairs potassium entry into cells, Adrenergic stimuli: (1) Beta-adrenergic stimuli enhance potassium entry into cells – it increases Na/K ATPase activity, and (2) alpha-adrenergic stimuli impair potassium entry into cells. pH: (1) Alkalosis enhances (2) acidosis impairs potassium entry into cells.

Further research should be warranted to properly quantify the effect of potassium shifts subsequent to the administration of insulin.