Do hERG blocking agents further increase the risk of sudden cardiac death in patients with type 1 diabetes?

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Introduction

- Type 1 diabetic patients have been shown to be at a higher risk of sudden cardiac death (SCD) and QTc prolongation may be a predisposing factor [1].In diabetic patients, QT interval prolongation due to hyperglycemia has been reported [2]. Extended periods of hyperglycemia occur regularly in diabetics [3].
- Moxifloxacin is a reversible blocker of both the rapidly and slowly activating delayed rectifier potassium channels in the heart, I_{Kr} and I_{Ks} meaning that it also prolongs QT, leading to a risk of cardiac arrhythmia [4].
- There is no safety warning to caution prescribers administering QT prolonging drugs to diabetic patients.
- In this study, we examine the effects of hyperglycemia on QTc and its subintervals in type 1 diabetic patients. We also investigate the interaction between a QT prolonging medicine and the hyperglycemic state in affecting the QTc interval.

Methods

- Single center, single-blinded, placebo-controlled, Phase I study in 22 type 1 diabetic patients over three days(10 males, 12 females).
- The study was approved by the local ethics committee South Central - Berkshire B Research Ethics Committee (NCT number: NCT01984827).
- Demographics: BMI 19.7 – 29.5, Age 20 – 36. Long term insulin regimes were maintained, except on study days.
- ECGs were recorded in triplicate and processed using the GE Healthcare Marquette 12SL ECG analysis program and the US Food and Drug Administration 510(k)-cleared GE research package QT GuardPlus.
- Time course analysis and concentration-effect modelling was used to assess the effect on QTc of glucose alone and in combination with moxifloxacin, and the effect of K^+.

Study design

Screening was from Day -21 to Day -2, Admission was on Day -1 (safety checks and eligibility)

Day 1

- -1H-0H baseline assessments
- 0H-1H dosing in the fasted state with oral glucose (75-150g, determined according to subject BM and insulin regime)
- 1H-2H hyperglycaemic clamp (intravenous glucose administration), titrating to target glucose concentration of 25 mmol/L.
- 1H-1:45H Moxifloxacin placebo (188mL normal saline) administered over 45 minutes.
- 2H IV insulin with potassium replacement
- Glucose and K^+ was monitored pre-dose and every 15 minutes from 0h – 2h, and every hour up to 6h (Dexcom G4 bedside glucometer and ABL90 FLEX PLUS blood gas analyzer). ECGs were recorded at the same time. 6H, 10H Meals were given.

Day 2 (as Day 1, except):

- No intervention, moxifloxacin placebo administered as per Day 1.

Day 3 (as Day 1, except):

- 1H-1:45H 300mg moxifloxacin was administered intravenously over 45 minutes in place of placebo, with a moxifloxacin PK sample taken (and samples for other parameters) at the same time points as glucose monitoring and ECGs.

Results

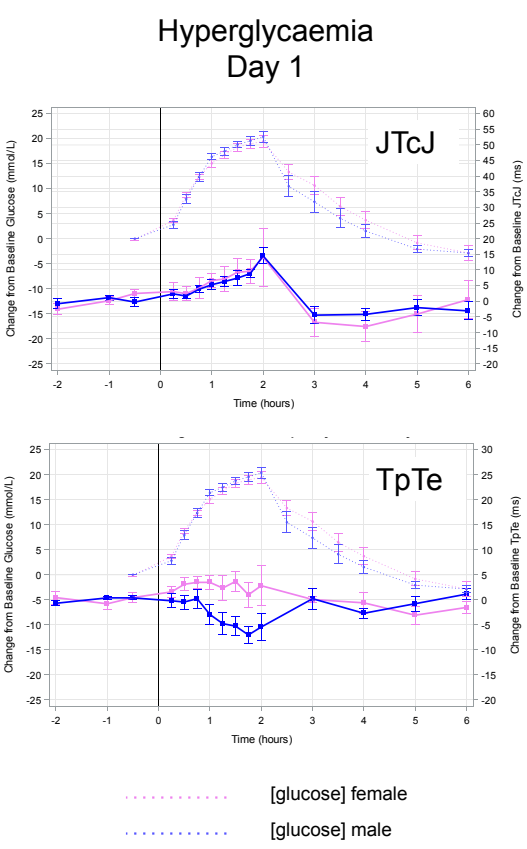

Figure 1: Time course plots of average glucose concentration and change from baseline of J-T_{peak} and T_{peak}-T_{end} by time point and drug administration (placebo or moxifloxacin). Vertical red line indicates the time of moxifloxacin application. Maximum observed mean moxifloxacin concentration was 2.34 µg/mL at 1:45H.

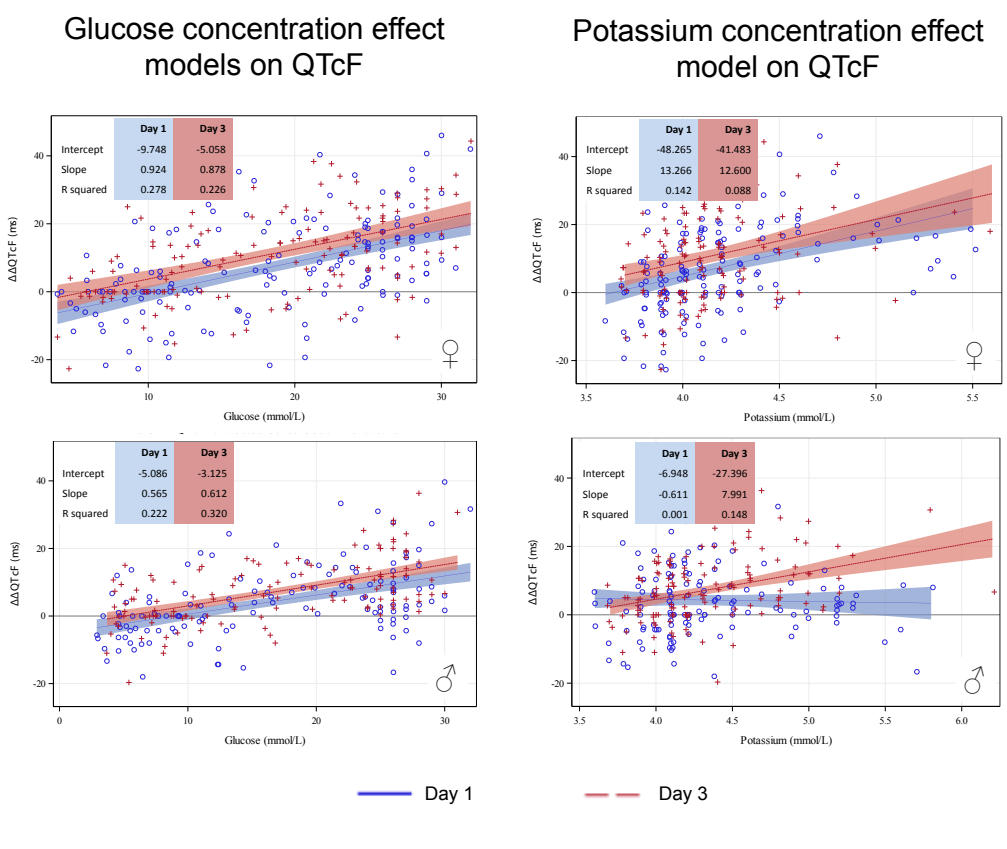

Figure 2: Concentration effect models showing the relationship between glucose concentration and QTcF duration, and between potassium concentration and ECG subinterval duration, in males and females

Summary of Conclusions

- **The data from this study suggest that QT prolonging drugs should be administered with caution to type 1 diabetic patients.** The key findings that support this conclusion are as follows:
  - A hyperglycemic state was seen to prolong the QTcF interval by a mean of 17 ms. In the time course analysis, hyperglycemia had a 10 ms greater QTc prolonging effect in female patients (21 ms) than males (11 ms). This sex difference arose from an inverse glucose concentration-dependent shortening of the T_pT_{end} interval in males during episodes of hyperglycemia that was not present in females.
  - Co-administration of moxifloxacin was observed to prolong the QTcF interval by a further 10 ms, leading to mean QTc prolongations of 27 ms. Maximum sustained QTc prolongations of up to 40 ms were observed in individual patients.
- There is a positive association between blood potassium concentration and QTcF interval prolongation.
- Increased blood K+ levels are correlated with QTc prolongation.
- There is a sex difference in regard to potassium glucose and QTcF prolongation: for men during hyperglycaemia no correlation between K^+ and QTcF can be seen
- The limitations of this study are: (i) the link between long QT and arrhythmias was not explored and to assess the risk of SCD will require further studies, (ii) only type 1 diabetics were studied, (iii) a small sample size, and (iv) the study did not randomise for long/short term insulin regimens.

References

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