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]. Blockade of I_{kr} by "hERG blocking" agents such as moxifloxacin also prolong 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 20 type 1 diabetic patients over three days. This is an interim analysis of 15 patients (8 males, 7 females).

The study was approved by the local ethics committee South Central - Berkshire B Research Ethics Committee (NCT number: NCT01984827).

Demographics: BMI 19.7 – 29.3, Age 21 – 32, 10 Caucasian, 1 black and 5 mixed race. Long term insulin regimes were maintained.

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 – 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 points.
- 6H, 10H Meals were given.

Day 2 (as Day 1, except):

- No intervention, moxifloxacin placebo administered as per Day 1.
- Insulin and glucose could be administered to maintain a constant glucose level.

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.

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.

Results

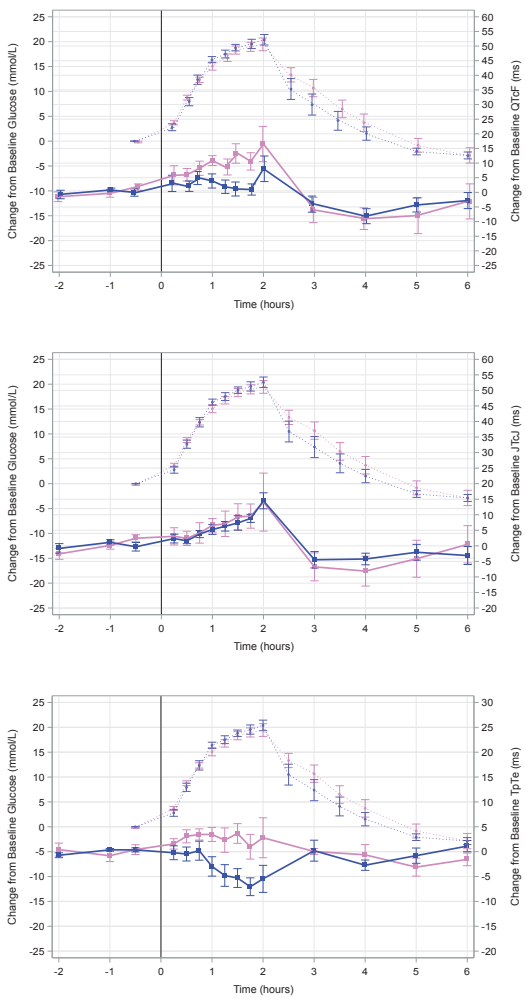

Figure 2: Time course plots of average glucose concentration and change from baseline of QTcF, J-T_{peak} and T_{peak}-T_{end} by time point and drug administration (placebo or moxifloxacin). Vertical red line indicates the time of moxifloxacin application. Maximum observed mean moxifloxacin concentration was 2.34 µg/mL at 1:45H.

Figure 3: Concentration effect model showing the relationship between glucose concentration and ECG subinterval duration, and between glucose and moxifloxacin concentration and ECG subinterval duration.

[glucose] female
[glucose] male
ECG subinterval change female
ECG subinterval change male

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 10.4 ms. In the time course analysis, hyperglycemia had a greater QTc prolonging effect in female patients than males. This 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 8 ms, leading to mean QTc prolongations of 18 ms, but maximum sustained QTc prolongations of up to 40 ms were observed in individual patients.
- The limitations of this study are: (i) the link between long QT and arrhythmias was not explored and the resulting risk for arrhythmias is unknown, (ii) type 2 diabetic patients, a much greater patient population, were not studied.

References

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