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 hyperglycaemia has been reported [2]. Extended periods of hyperglycaemia occur regularly in diabetics [3].
- Moxifloxacin is a reversible blocker of both the rapidly and slowly activating delayed rectifier potassium channels in the heart, TpTe and TwpTm, 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 hyperglycaemia 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: NCT01966527).
- Demographics: BMI 19.7 – 29.5, Age 20 – 35. Long term insulin regimens were maintained, except on study days.
- ECGs were recorded in triplicate and processed using the GE Healthcare Marquette 125L 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
  - 0H-0H (daying in the fasting state with oral glucose (75-150g, determined according to subject BMI 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 (Dascom G4 bedside glucose meter and ABUSI 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: 30mg 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 JTcF and TpTe 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 hyperglycaemic state was seen to prolong the QTcF interval by a mean of 17 ms. In the time course analysis, hyperglycaemia 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 TpTe interval in males during episodes of hyperglycaemia 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.

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References