Sex Hormones and the QT Interval: J-T_{peak} and T_{peak}-T_{end} Assessment and Further Insights Into the Physiological Effects

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Introduction

QTc intervals are longer in women than in men. Females have been shown to have a higher risk of Torsades de Pointes. - this sex difference is apparent only after puberty suggesting a role of sex hormones [1]. The effect of sex steroid hormones on cardiac repolarization, mainly estradiol, progesterone and testosterone, has been suspected but the mechanisms involved in the modulation of cardiac repolarization are still not completely clarified [2]. This study aimed to assess whether there is a reliable evidence for a menstrual cycle influence on QTc. The goal is to provide further mechanistic insights into hormonal control of human ventricular repolarization and influence of gonadal hormones on different ion channel currents.

Methods

This was a randomised, Phase 1 study, primarily designed to assess the safety, tolerability, pharmacokinetic and pharmacodynamic effects of a novel IMP in healthy female participants of childbearing potential that required a run-in period for the synchronisation of all females menstrual cycle (Figure 1). The study was approved by the local ethics committee South Central - Berkshire B Research Ethics Committee (EudraCT Number: 2018-003702-36). This report describes the relationship between QTcF and levels of estradiol and progesterone during the study. The IMP was known to have no effects on QTc.

Baseline was defined as the pre-dose value of Day 1 for hormone data and as the mean of the three pre-dose timepoints for ECG parameters. For the by time-point analysis Day 2 data were summarised, however for the model based analysis, Day 2 data were excluded. Here, data from 42 females is reported. To investigate the role of hormone levels (estradiol and progesterone) on the QT interval in the normal menstrual cycle, an analysis of ECG variables was performed in combination with sex hormones using concentration effect modelling.

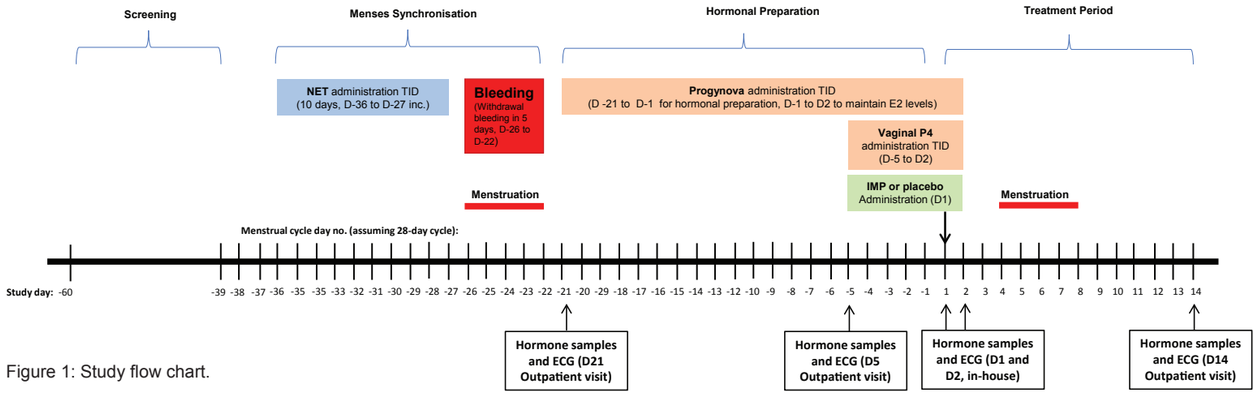

Figure 1: Study flow chart.

Conclusions

- This study showed a significant influence of estradiol on QTcF, but no significant influence of progesterone. The assessment of estradiol on J-T_{peak} and T_{peak}-T_{end} is ongoing.
- The estimate for the influence of estradiol during the menstrual cycle on QTcF was 0.017 msec per ng/L.
- The limitations of this study are that the assessment of the IMP required hormonal preparation, using progynova and utrogestan. These drugs may have may have limited the ability to observe estrogen-induced changes on QTc over the course of the natural menstrual cycle: progynova's active ingredient is estradiol valerate, which is biologically equivalent to endogenous estrogen. Utrogestan is known to increase progesterone levels [3].
- This was a hypothesis-generating work that demonstrated two things: Firstly, females are needed in TQT studies to identify any sex differences for a given drug. Secondly, research is needed to better understand the mechanism responsible for females being at greater cardiac risk.

References

[1] Rautaharju PM, Zhou SH, Wong S. et al. Can J Cardiol.1992;8:690-695.
[2] Furukawa T, Kurokawa J. Pharmacol Ther. 2007; 115(1):106–115.
[3] Emi R et al. J Gynecol Obstet Biol Reprod (Paris). 1989;18(2):229-34.

Results

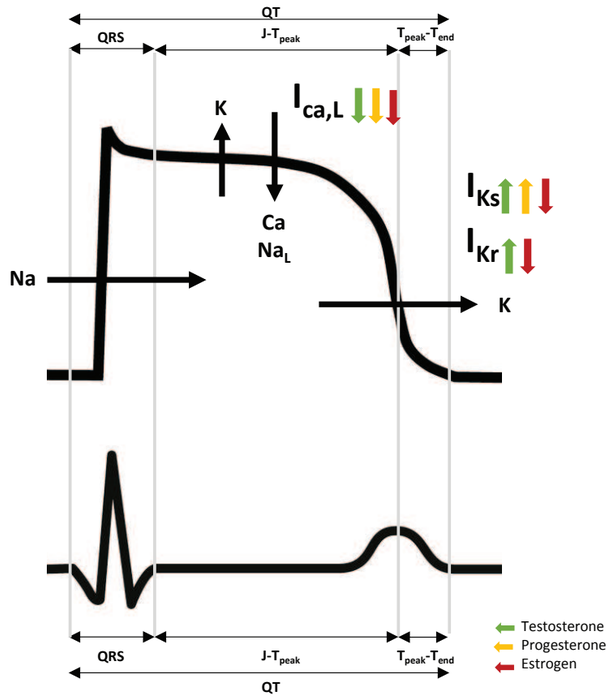

Figure 2: The effect of sex hormones on AP and ECG. Estrogen lengthens the QTc, while testosterone and progesterone shorten ventricular repolarization.

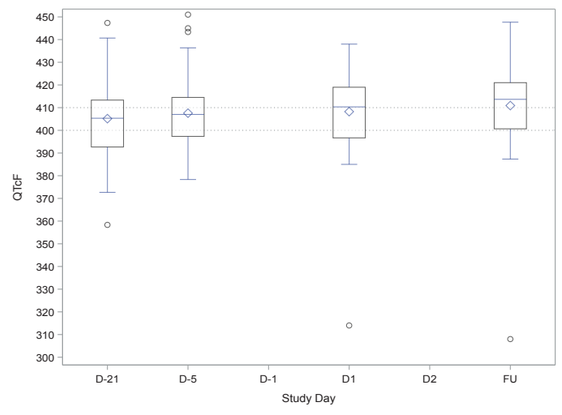

Figure 3: Mean QTcF for each study day and changes from baseline for estradiol and progesterone.

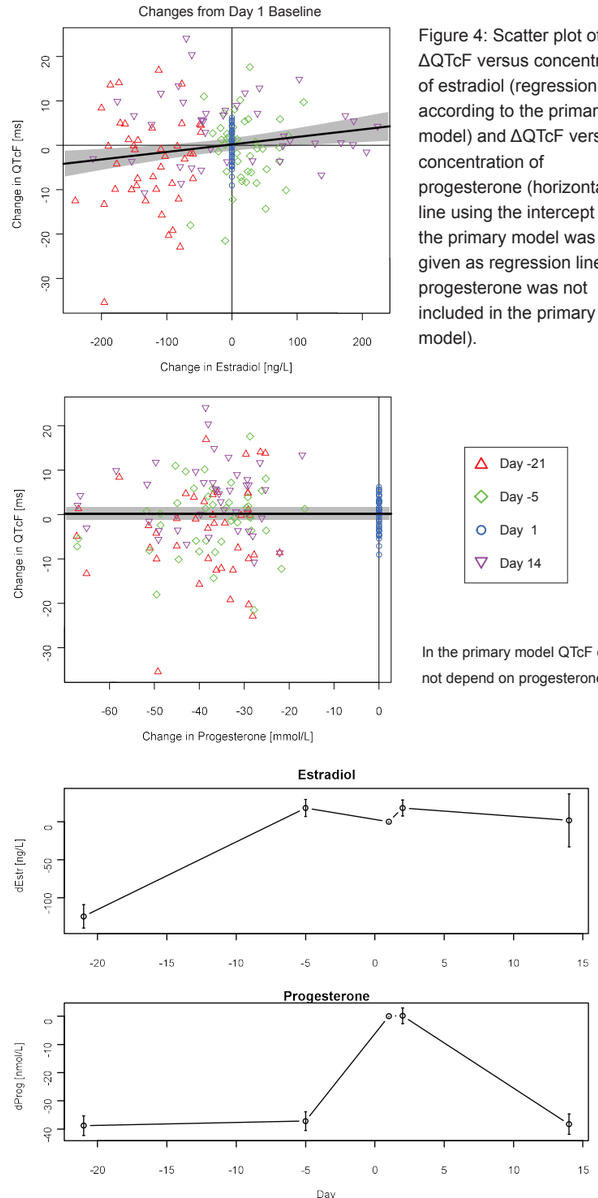

Figure 4: Scatter plot of ΔQTcF versus concentration of estradiol (regression line according to the primary model) and ΔQTcF versus concentration of progesterone (horizontal line using the intercept of the primary model was given as regression line as progesterone was not included in the primary model).

In the primary model QTcF does not depend on progesterone.

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