Effects of progesterone and estradiol on QT subintervals over the course of a menstrual cycle

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Introduction

QTc intervals have been observed to be longer in women than in men and this sex difference is apparent only after puberty, which suggests that sex hormones play a role [1]. The effect of sex steroid hormones on cardiac repolarization, mainly estradiol, progesterone and testosterone, has long been suspected but the mechanisms involved in the modulation of cardiac repolarization have not yet been completely clarified [2]. This study aimed to assess whether there is a reliable evidence for the influence of a menstrual cycle on the duration of cardiac subintervals. 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 female participants' menstrual cycles (Figure 1). The study was approved by the local ethics committee South Central - Berkshire B Research Ethics Committee (EudraCT Number: 2018-003702-36). This study showed that the tested IMP had no effects on QTc, and those data are not reported here.

The study was conducted in 45 women, aged 20-37, with a BMI between 16.5 and 29.9 kg/m2. Intensive cardiac assessments were conducted and levels of estradiol and progesterone were measured in blood drawn on Days -21, -5, 1, 2 and 14 to examine the relationship between sex hormones and QT/QTc. ECG recordings were taken after a meal on Days -21, -5 and 14 in order to reduce bias for diurnal QTc variation.

All ECG recordings were obtained in triplicate performed at one-minute intervals over three minutes for each time point to confirm accuracy and precision of measurements. The effects of a meal on the ECG were used to establish assay sensitivity. Concentration-effect modelling was conducted to explore the effects of progesterone and estradiol separately on cardiac subintervals. Linear mixed effects models were fitted to the ECG analysis data and the effect on heart rate and cardiac subintervals were estimated using the estradiol-change-from-baseline and the progesterone-change-from-baseline as parameters.

Results

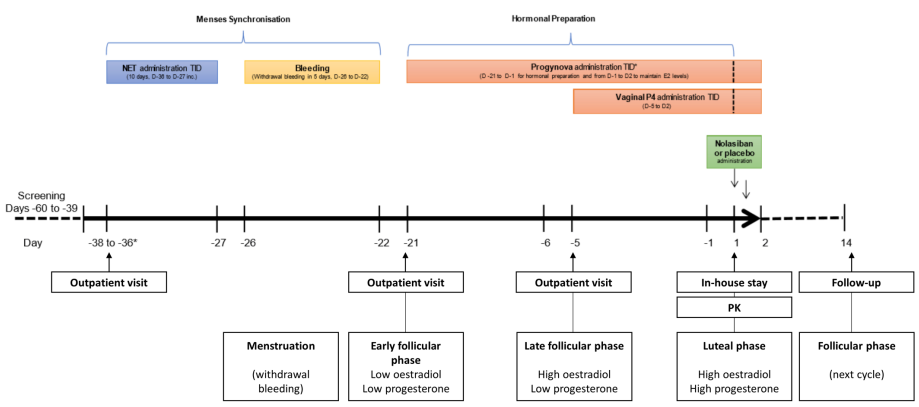

Figure 1: Study design.

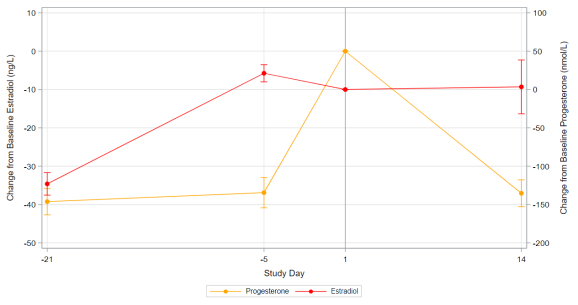

Figure 3: Changes from baseline for estradiol and progesterone.

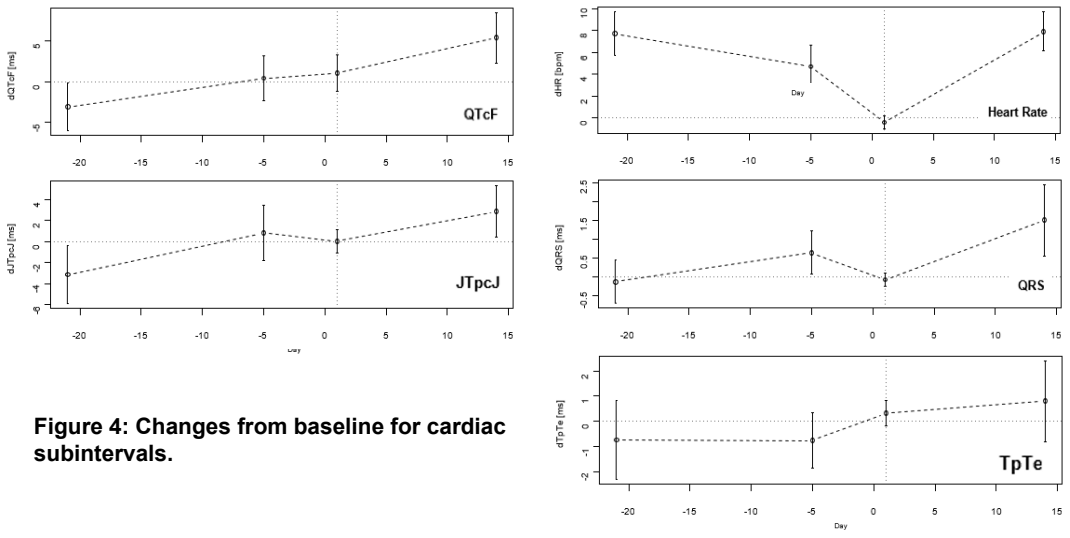

Figure 4: Changes from baseline for cardiac subintervals.

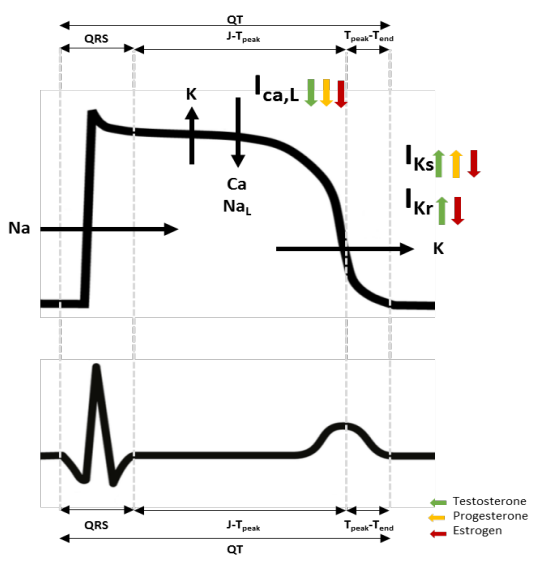

Figure 2: The effect of sex hormones on AP and ECG. Estrogen lengthens the QTc, while testosterone and progesterone shortens ventricular repolarization.

Table 1: Significant estimates of fixed effects of sex hormones on cardiac parameters.

Parameter	Model	AIC	Effect	Effect estimate	SE	d.f.	T value	90% CI	
Heart rate	Progesterone, without baseline	1065.8	Progesterone [ms per nmol/L]	-0.158	0.0218	Inf	-7.23	-0.194	-0.122
			Intercept [ms]	0.5	0.82	Inf	0.59	-0.9	1.8
QTcF	Oestradiol without baseline	1225.5	Oestradiol [ms per ng/L]	0.013	0.0080	Inf	1.58	-0.001	0.026
			Intercept [ms]	1.3	0.91	Inf	1.41	-0.2	2.8
QRS	None	726.5	Intercept [ms]	0.5	0.21	Inf	2.28	0.1	0.8
JTpc	Oestradiol without baseline	1144.8	Oestradiol [ms per ng/L]	0.020	0.0060	Inf	3.41	0.011	0.030
			Intercept [ms]	0.7	0.85	Inf	0.81	-0.7	2.1
TpTe	Baseline only	940.5	Baseline [ms per ms]	-0.16	0.056	Inf	-3.19	-0.27	0.09
			Intercept [ms]	-0.1	0.39	Inf	-0.25	-0.7	0.5

Summary of Conclusions

- This study showed a significant positive effect of estradiol on QTcF (0.013 ms per ng/L), which was driven by a positive effect of estradiol on JTpcJ (0.020 ms per ng/L). We hypothesise that this is due to the down regulation of I_{Ks} and I_{Kr} reducing repolarisation reserve.
- There was significant negative effect of progesterone on heart rate (-0.158 ms per nmol/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. Further work should be conducted to determine if the relationships between cardiac subinterval duration and hormone levels are direct or indirect.

References

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[3] Emi R et al. J Gynecol Obstet Biol Reprod (Paris). 1989;18(2):229-34.