

Influence of calcium blockade on the QT effects of a meal

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Introduction

Food ingestion in healthy volunteers leads to an increase in heart rate cardiac stroke volume. The ECG shows QTc interval shortening from a fasting baseline up to 7 hours. The food-induced shortening of the QTc interval was correlated with a rise of C-peptide [1] but other mechanisms may be responsible. Recently, we have shown that the QT effects of a meal are due to shortening of the J-T_{peak} subinterval which correlates to the plateau phase or phase 2 of the cardiac myocyte action potential [2].

Prior observations indicate that calcium block primarily affects early repolarization by shortening the J-T_{peak}c interval [3, 4].

The aim of the present study was to investigate whether the effects of a meal on the J-T_{peak} interval are ameliorated by a calcium blocker. Verapamil was used in this study which is known to block Ca²⁺ channels (both L- and T- type) as well as I_{kr} with no effects on the I_{Ks} channel [5]. A sex subgroup analysis was also conducted. The effects of verapamil on I_{kr} channels was clearly demonstrated validating the results.

Methods

This was an open-label study in 20 healthy Caucasian male (n=12) and female subjects (n=8). On Day -1 subjects received a standardised meal and from Day 1 verapamil (80 mg) was administered every 8 hours daily for 8 days. ECGs were recorded on Days -1, 1 and 8. Validated algorithms for the measurement QT sub-intervals were used and the effects over time were analysed.

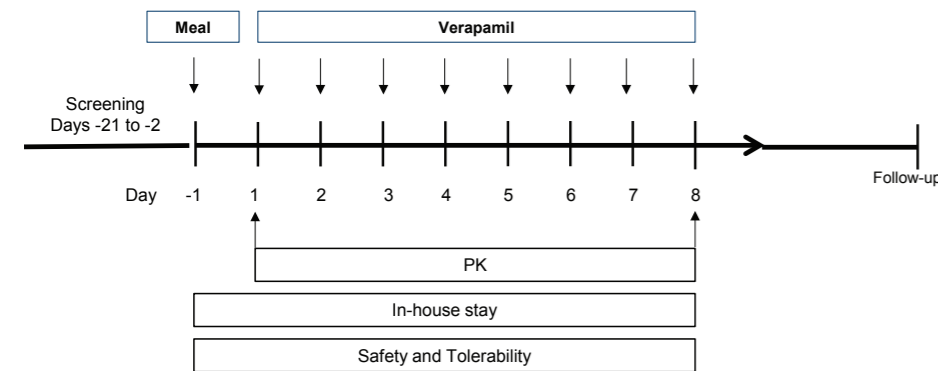


Figure 1: Study flow chart.

Results

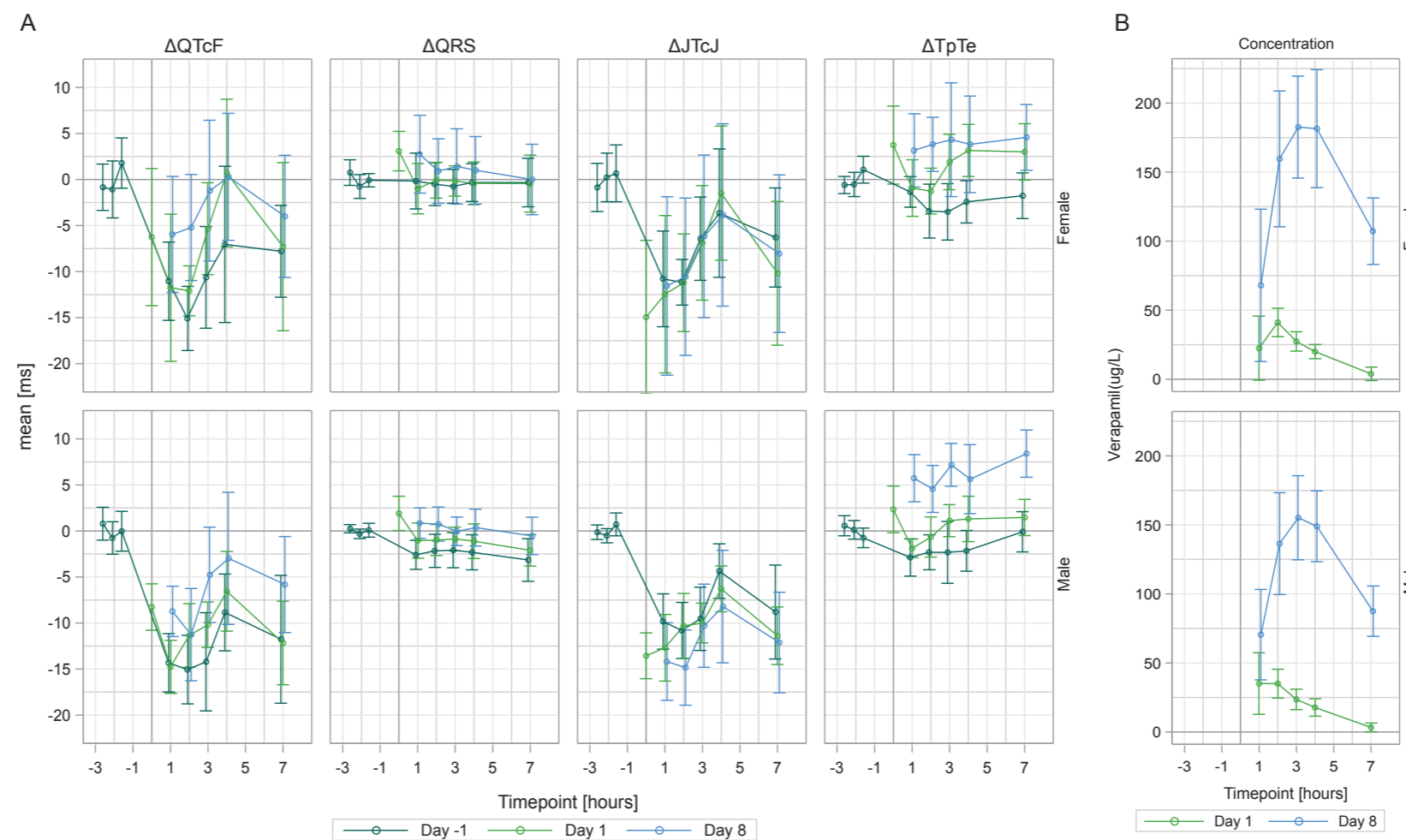


Figure 2: A) Time course of QTcF, QRS, J-T_{peak}cJ (Δ JTcJ) and T_{peak}-T_{end} (Δ TpTe). Vertical bars represent 90% confidence interval. B) Time course of plasma concentrations (mean ± 90% confidence intervals) for verapamil on Day 1 (80 mg) and Day 8 (80 mg every 8 hours for 8 days).

Table 1: Mean and 2-sided 90% confidence intervals of the mean for Δ QTcF, Δ QRS, Δ J-T_{peak}cJ and Δ T_{peak}-T_{end} at the observed peak effect at 2 hours.

Peak effect at 2h	Females	Males
QTcF ms (90%CI)		
Day -1	-15.1 (-18.6; -11.6)	-15.1 (-18.8; -11.3)
Day 1	-12.1 (-14.8; -9.4)	-11.3 (-14.8; -7.9)
Day 8	-5.2 (-11.0; 0.5)	-11.3 (-16.3; -6.3)
QRS ms (90%CI)		
Day -1	-0.5 (-2.8; 1.8)	-2.2 (-4.0; -0.4)
Day 1	-0.1 (-2.0; 1.9)	-1.0 (-2.7; 0.7)
Day 8	0.9 (-2.6; 4.4)	0.7 (-1.1; 2.6)
J-T_{peak} ms (90%CI)		
Day -1	-11.2 (-13.6; -8.7)	-10.8 (-13.8; -7.8)
Day 1	-11.2 (-16.5; -5.9)	-10.3 (-13.8; -6.8)
Day 8	-10.6 (-19.1; -2.0)	-14.8 (-18.9; -18.9)
T_{peak}-T_{end} ms (90%CI)		
Day -1	-3.4 (-6.4; -0.5)	-2.3 (-5.7; 1.0)
Day 1	-1.3 (-3.8; 1.2)	-0.7 (-2.8; 1.5)
Day 8	3.8 (0.9; 6.8)	4.6 (2.0; 7.1)

Discussions and conclusions

References

- This study confirmed that a meal leads to a significant shortening of QTcF and J-T_{peak} in both male and female subjects. No significant changes were seen in QRS or T_{peak}-T_{end} [2].
- Females had a more pronounced effect on QTcF and J-T_{peak} while T_{peak}-T_{end} values higher in males.
- Verapamil did not appear to ameliorate the effect of a meal on J-T_{peak}. Verapamil was shown to slightly increase QTcF and T_{peak}-T_{end} accompanied by a J-T_{peak} shortening on both Days 1 and 8.
- These results are in line with what it was observed in the study reported by Vicente et al [6] whereby the verapamil effects on the QTc interval and subintervals were investigated after a single dose of 120 mg. In the same study Vicente et al showed no systematic sex differences in the ECG subintervals despite the maximum plasma drug concentration of verapamil being higher in females than in males.
- Verapamil was well-tolerated in accordance with its safety information and all adverse reactions were mild and resolved.
- The limitation of this study is that it was not powered to detect sex differences or exposure-response relationship due to its small sample size. The difference between males and females in the observed induced effects should be interpreted with caution as they are only descriptive.
- Overall conclusion:** The results from this study suggest that the mechanism by which food affects J-T_{peak} is not affected by Ca²⁺L channel block, suggesting that the mechanism involved in the QTc shortening after a meal is not related to Ca²⁺L channels.

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