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**Sensitivity of T-Wave Morphology and the QT Interval to Small Drug-Induced ECG Changes**

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The electrocardiographic QTc interval is used to assess cardiac safety in drug trials but it can be difficult to separate subtle drug-induced effects on QTc from the spontaneous variability that is observed in QTc intervals. The present study focuses on the merits of a quantitative assessment of changes in T-wave morphology after administration of an I\textsubscript{Kr} channel inhibiting compound.

Seventy-nine healthy subjects were included in this study. After a baseline day where no drug was given, forty subjects received an I\textsubscript{Kr} blocking anti-psychotic compound (Lu 35-138) on 7 consecutive days while thirty-nine subjects received placebo. Resting ECGs were recorded and used to calculate a principal component median beat from independent leads (I, II, V1-V6). The principal component T-wave was used to determine a combined measure of repolarization morphology (MCS), based on asymmetry, flatness and notching. Effect sizes for MCS and the Fridericia corrected QT interval (QTcF) were determined on the final study day (0, 2, 4, 6 and 12 h post-dose) as the time matched placebo corrected changes of means from baseline expressed in number of standard deviations at baseline.

The placebo corrected mean change in QTcF reached a plateau of 18 ms at 4 h post-dose whereas changes in MCS continued to increase for an additional 2 h. The placebo corrected effect sizes for MCS (1.15, 1.56, 1.80, 1.92, 1.45) were 1.8 times larger than those for QTcF (0.71, 0.76, 1.03, 0.98, 0.88), p=0.0013. At maximum individual change from baseline the placebo corrected effect size for MCS, 2.01 (95% CI: 1.44 to 2.58) was 2.18 times larger than for QTcF, 0.92 (95% CI: 0.60 to 1.24), p<0.001. MCS predicted drug changes from placebo changes with an area under the receiver-operating curve of 0.923 (95% CI: 0.897 to 0.949) compared to QTcF 0.875 (95% CI: 0.841 to 0.909).

For Lu 35-138, the appearance of abnormal T-waves on the ECG was a more sensitive marker of drug induced changes than QT interval prolongation. The effect size measure provided evidence that T-wave morphology has a lower variability at baseline and a larger difference between baseline and treatment means than the QT interval.