Effects of Common Confounders on JTp and Tpe as Novel Proarrhythmia Biomarkers

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INTRODUCTION

QTc was identified as a central proarrhythmic risk biomarker in ICH S7A but recent clinical data have revealed limitations when using QTc mostly related to false positives. Drugs with balanced multi-ion channel inhibition were shown to prolong QTc without increased proarrhythmic risks. Research led by the US FDA has identified JTp as an alternate ECG biomarker to evaluate drug-induced proarrhythmic risk in clinical trials and HESI showed similar results in canines and non-human primates. In humans or non-clinical species, proarrhythmic drugs are associated with an increase in QT but also JTp. The current study evaluated the effects of common ECG confounders (body temperature, stress and time of day) on QTca, JTpca and Tpeca.

METHODOLOGY

Beagle dogs were anesthetized with isoflurane and subjected to progressive hyperthermia (42°C), hypothermia (33°C) (n=4) or epinephrine IV injections (0.03 mg/kg) (n=9). All ECG parameters (QTca, JTpca and Tpeca) were subjected to individual rate correction. Control telemetry data obtained over at least 24 hours from Beagle dogs (n=8) and cynomolgus monkeys (n=8) were used to evaluate circadian cycle effects and heart rate to ECG parameter relationships.

RESULTS

QTca (slope -12.57 msec/degree Celsius) and JTpca (-14.79 msec/degree Celsius) durations were negatively correlated with core body temperature. However, Tpeca was minimally affected (1.50 msec/degree Celsius). Epinephrine was associated with QTca and JTpca shortening followed by a slow recovery. This could be related to under-correction in the presence of rapid changes in heart rate and hysteresis. Minimal effects were noted on Tpeca. The slopes for QTca, JTpca and Tpeca relative to heart rate were similar between day and night time.

CONCLUSION

The above results highlight the importance of potential confounders on the traditional ECG biomarker QTc but also on JTpca and Tpeca. These potential confounding effects need to be considered in the interpretation of ECG biomarkers during proarrhythmic risk assessment in non-clinical drug development.
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- General toxicology in all species
- Special toxicology
  - Inhalation
  - Dermal
  - Oral
  - Immunotoxicology
  - Regenerative medicine
  - Reproductive toxicology including minigrids and NHPs
  - Carcinogenicity studies also in rast12 and p33+/− mice
- Genetic toxicology: ICH compliant
  - Package
  - In vitro toxicology: BCCP, h-CLAT, KaratinoSens™, DPRA, Photo 3T3-NIH, EpiSkin™, chicken eye test
  - Agrochemical / chemical / REACH
  - QSAR
  - Physico-chemical testing
  - Ecotoxicology: wide range of test species

SAFETY PHARMACOLOGY
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  - CV (JET), BP
  - Respiratory (JET), plethysmography
- CNS (FOB) and JET-EEG

MEDICAL DEVICE
- Biocompatibility testing
- Cardiovascular stents, electrophysiology and structural heart studies
- Long-bone defects and cranio-maxillofacial/dental models
- Spinal fusion models
- Joint and cartilage repair models
- Regenerative medicine (growth factors, biomaterials, cell and gene therapy)

DMPK, BIOANALYSIS, BIOMARKERS
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- Toxicogenomics, miRNA: Affymetrix accredited service provider, next generation sequencing (Illumina)
- Immunology: 10-color flow cytometer, Luminex, Iaso Scale

SPECIALIZED EXPERTISE
- Juvenile studies including minigrids
- Ototoxicity in rats
- Fertility studies in rodents and NHPs
- Radiation safety and efficacy studies
- Tissue Cross Reactivity (TCR): human and animal tissue banks
- Gene therapy vector biodistribution via qPCR
- ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
- Lead optimization and predictive toxicology services: Leadscreen™

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