Beyond QT interval in drug safety Assessment

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Disclosures

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Part 1: the mechanisms (and some measurements)
- KvLQT1 and HERG mutations (LQT1/LQT2) are associated with a reduction of the slowly and rapidly activating delayed repolarization $K^+$ currents ($I_{Ks}$, $I_{Kr}$).

Long QT syndrome
QT interval distribution in LQT1 and LQT2

QT prolongation is the only ECG marker used for assessing the level of cardiotoxicity of new drugs. But it is recognized as an imperfect surrogate marker of an increased risk for cardiac arrhythmias.

“…the risk of torsades de pointes is not a linear function of the QT interval, nor of the extent of the QT-interval prolongation during drug therapy.”

T wave morphology in the inherited forms of the long QT syndrome


Drug induced T wave morphology changes

- T wave changes in subject receiving Moxifloxacin 400 mg vs. Sotalol 160 mg and Sotalol 320 mg

Modeling Approach

Cell-to-ECG model

Correlation ECG parameters to TDR from the Model

Drug data & biomarker evaluation
Repolarization Hetero vs. ECG Morphology changes

Increase of dispersion
Cause:

- Flatness of T wave
- T wave notch
- T wave symmetric change
- Tpeak to Tend change
  - How to measure the T peak?

Representative Aps of endo, M, epi layers

Vector magnitudes of 12 lead ECGs, 6 settings

Baseline: Representative Aps of endo, M, epi layers

New T Wave Morphology Parameters

a: QT and subintervals
b: Flatness, asymmetry and notching

- QRS
- J-T_peak
- T_peak
- T_end
- QT

Flat
Asymmetric
Notched

Gaussian modeling

- Mean T wave vector
- Mean QRS vector
- Ventricular gradient

LRD30%
ERD30%

- T-wave loop
- PCA1
- PCA2

- 30% of repolarization duration
d: Vectorcardiographic biomarkers

Thanks Jose Vicente of FDA for providing the image
T wave morphology: Which ECG features to use?

- Tpeak: Which peak?
- T wave shape: What shape descriptors?

12 leads

VM

Tp dominant by large amplitude lead

Tp large discrepancy among leads
New T Wave Morphology Parameters

New T wave morphology parameters, cont