Some results and thoughts on QT studies

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Topics

- Introduction - History
- End of T-wave
- A better parameterization
- Use of a positive control
- Good faith needed
History

- Seldane alone – 60mg BID – 6-12 msec
- Seldane + Terfenadine = 10 deaths!

!!! Interaction !!!

Seldane and Terfenadine
hERG ion channel
Bound inhibitor

Anti-psychotic examples
FDA dictated Pfizer study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline Mean</th>
<th>Change at Steady State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone (N=31)</td>
<td>402.1</td>
<td>20.3</td>
</tr>
<tr>
<td>Risperidone (N=20)</td>
<td>396.3</td>
<td>11.6</td>
</tr>
<tr>
<td>Olanzapine (N=24)</td>
<td>397.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Quetiapine (N=27)</td>
<td>398.0</td>
<td>14.5</td>
</tr>
<tr>
<td>Thoridazine (N=30)</td>
<td>395.9</td>
<td>35.6</td>
</tr>
<tr>
<td>Haloperidol (N=20)</td>
<td>394.7</td>
<td>4.7</td>
</tr>
</tbody>
</table>

(Some deaths with Thoridazine.)
ECG wave form


American Heart Journal 1996

Arrhythmias

Dose-response relation between terfenadine (Seldane) and the QTc interval on the scalar electrocardiogram: Distinguishing a drug effect from spontaneous variability
QT variation, normals

QT Variation, diseased
What matters?

- Absolute magnitude
- Outside personal range
- Subcomponent of wave form
- Interaction with nutrition
- Interaction with genetics
- Interaction with drugs
- Etc.

The heart is complex
Marking the ends of T-waves:
algorithms and experts

Zhou and Sedranski (2009)

Textbook versus Reality
Expert Variability for End of T

Marking the end of a T-wave

Two experts marked two beats rather differently.
Differences between two experts

NB: experts are not consistent. Massive variability.

End of T-wave

- selected beats of data show that the difference between two experts’ marks can easily exceed 10 milliseconds
- experts appear to use the slope and curvature of the waveform differently in judging the end of the T-wave.
Bayesian, use slope and curvature

- Just as consistent as experts
- Can be automated
- Much more cost effective

NISS study of T-wave shape

FUNCTIONAL DATA ANALYTIC APPROACH OF MODELING ECG T-WAVE SHAPE TO MEASURE CARDIOVASCULAR BEHAVIOR

BY YINGCHUN ZHOU AND NELL SEDRANSK

Cardiac safety testing on two points of the ECG waveform:
1. Onset of the Q-wave and termination of the T-wave; and
2. Only a few beats are measured.
Four parameters

T-wave, Four Beats

Dashed line, reference curve
u, d, h, m relation to QT

Detecting a problem
Easy to detect with 4-parameters

u, d, h, m relative to RR
Lags are usually ignored!

Correlation between the estimated model parameters and current and previous RRs

<table>
<thead>
<tr>
<th>RR</th>
<th>( t )</th>
<th>( t - 1 )</th>
<th>( t - 2 )</th>
<th>( t - 3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \hat{a} )</td>
<td>-0.3216</td>
<td>-0.4003</td>
<td>-0.7554</td>
<td>-0.3152</td>
</tr>
<tr>
<td>( \hat{d} )</td>
<td>-0.4580</td>
<td>-0.6309</td>
<td>-0.7428</td>
<td>-0.3957</td>
</tr>
<tr>
<td>( \hat{m} )</td>
<td>0.3009</td>
<td>0.3419</td>
<td>0.4596</td>
<td>0.1900</td>
</tr>
<tr>
<td>( \hat{h} )</td>
<td>0.2410</td>
<td>-0.1825</td>
<td>-0.3977</td>
<td>0.0605</td>
</tr>
<tr>
<td>QT</td>
<td>-0.0478</td>
<td>0.1953</td>
<td>0.1646</td>
<td>-0.0455</td>
</tr>
</tbody>
</table>

Need good faith on both sides

- Multiple testing
- Continued use of positive control
- Setting Mean at 5msec and UB at 10 msec (any small bias will mess things up)
- Correction formula
- Select single time point based on blood levels
- Selection of two points, QT, likely stifled innovation
Positive control necessary?

- To date, drug-induced torsade de pointes has consistently involved blockade at the IKr, (HERG).
- hERG prediction well-studied – G 90k hits
- hERG is designed and counter screened out

Positive Control

Qian Liu and Ying Jun Cao
Positive Control in a "Thorough QT/QTc Study"
*J Clin Pharmacol January 5, 2011*

Nevertheless, the value of the positive control in a negative thorough QT study is limited.
## Logic Table

<table>
<thead>
<tr>
<th>Scenario</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trt Upper bound</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&lt;10</td>
<td>&lt;10*</td>
</tr>
<tr>
<td>Pos Control</td>
<td>&gt;5</td>
<td>&lt;5</td>
<td>&gt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Study Conclusion</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
</tr>
</tbody>
</table>

*Retrospective power

## Dead in Bed

- Dead in Bed Syndrome (GN – 94k)
- Common in Type 1 diabetes
- Unknown etiology – perhaps arrhythmia?
- Do diabetics have prolonged QT?
- What is the effect of insulin on QT?
- Is some heart energy disruption happening?
- Heart energy metabolism complex
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