Background

- The QT interval is a surrogate marker for proarrhythmic risk and is regularly assessed in preclinical cardiovascular safety studies (CVS).
- A QT prolongation of 2-5 ms in the dog can lead to a relevant 10 ms effect in human\(^1,2\).
- PKPD analysis is not regularly used in preclinical CVS but could ease translation to humans.

Methods

- A realistic “true” PKPD model (Tab-1) was developed using data from vehicle arms of 28 CV studies and a sotalol study (positive control).
- QTc = individual heart rate corrected QT interval
- \(QT_c(t) = BL + A \cdot \cos \left( \frac{2\pi}{24} \cdot (t - \varphi) \right) + \frac{E_{\max} \cdot C(t)^\gamma}{EC_{50} + C(t)^\gamma} \)

The “true” PKPD model was used to simulated repeatedly (100x) CVS with decreasing dose intensities producing typical drug-induced ΔQTc at high-dose \(C_{max} = 0-12\) ms (Fig-1).

Each simulated study was analysed for drug effects using both PKPD and ANCOVA analysis and power was calculated (Fig 1):

| Parameter                  | Typical value | BSV/IOV (CV\%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline QTc, BL [ms]</td>
<td>254</td>
<td>5.6/1.4 ms</td>
</tr>
<tr>
<td>Amplitude A [ms]</td>
<td>1.7</td>
<td>±1.7 ms</td>
</tr>
<tr>
<td>Shift (\varphi) [h]</td>
<td>19</td>
<td>11%</td>
</tr>
<tr>
<td>(E_{\max}) [ms]</td>
<td>50</td>
<td>27%</td>
</tr>
<tr>
<td>(EC_{50}) [ng/ml]</td>
<td>2370</td>
<td>43%</td>
</tr>
<tr>
<td>Hill coefficient, (\gamma)</td>
<td>1.2</td>
<td>29%</td>
</tr>
</tbody>
</table>

Tab.1. Parameters from “true” PKPD model used for study simulations.

BSV/IOV: between-subject/inter-occasion variability. Residual: ±6.2 ms

Objectives

- To investigate the power of population PKPD analysis to detect different magnitudes of QT-prolongation in the conscious telemetered dog.
- To compare the power and estimated drug effects with conventional statistical analysis (analysis of covariance, ANCOVA)\(^3-5\)

Results

Power: PKPD analysis had a power of \(\approx80\%\) to detect a ΔQTc of 4 ms, ANCOVA only \(\approx50\%\) (Fig-2, left).

False-positive rate: higher by ANCOVA (40%) than by PKPD (< 5%).

Dose-effect relationship: similar estimates from PKPD analysis and ANCOVA.

Conclusions

- PKPD analysis showed very good power to detect small magnitudes of QTc prolongation in a typical preclinical setting. Compared to traditional ANCOVA superior power was observed.
- These results underscore the its value in preclinical safety testing. Sensitivity of estimates to PK profiles, number of PD sampling times / individuals should be tested.

References

1. Chain A et al., Br J Clin Pharmacol 2013
2. Leishman DJ et al., J Pharmacol Toxicol Methods 2012
3. Ayloot M et al., Pharm Stat 2010
5. Jivarajah A et al., J Pharmaco Toxicol Methods 2010