Evaluation of Clinically-Relevant Proarrhythmic ECG Biomarkers in Conscious Beagle Dogs, Using a Newly Developed Multiple Lead ECG Telemetry Implant

Abstract
Preclinical proarrhythmia risk assessment of multiple ion channel inhibitors (ICIs) and other small molecules often relies on in vitro safety pharmacology (SP) models. Combined efforts to develop preclinical in vivo tools are essential to provide better dosimetric and pharmacodynamic information to guide clinical development. The purpose of this study was to evaluate the potential proarrhythmic risk of a preclinical in vivo tool, the Stellar/TSE 5-Lead ECG Implant. This was accomplished using a validated in vivo method for proarrhythmic risk assessment: telemetry monitoring of ECG morphology for 1-4 hours postdosing. Novel Stellar/TSE implants were designed specifically to record simultaneously 5-lead ECGs: Lead I, II, III, and 2 precordial leads. The inclusion of precordial leads, alone or as part of a vector magnitude, may enable better assessment of enhanced ECG morphology assessments in SP, toxicology, and/or combined SP-toxicology studies.

METHODS

• Male beagle dogs (8-10 kg, N=5) were instrumented with Stellar/TSE telemetry implant. Novel Stellar/TSE implants were designed specifically to record simultaneously 5-lead ECGs: Lead I, II, III, and 2 precordial leads that were implanted as I, II, and V1, serving as VM II I III or VM II I V1 after filtering channels to maintain stable zero baseline. Data were reported as beat-to-beat or binned in 15- or 60-min time periods within animal studies. Beagle dogs were telemetered animals, and study, then averaged to determine mean ± SE

RESULTS

• Baseline ECG data were from vehicle study (N=5)

<table>
<thead>
<tr>
<th>ECG Interval</th>
<th>Vehicle, Mean ± SE</th>
<th>Dofetilide, Mean ± SE</th>
<th>Verapamil, Mean ± SE</th>
<th>Mexiletine, Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR (msec)</td>
<td>180 ± 10</td>
<td>200 ± 15</td>
<td>190 ± 10</td>
<td>190 ± 10</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>400 ± 20</td>
<td>420 ± 25</td>
<td>410 ± 20</td>
<td>410 ± 20</td>
</tr>
<tr>
<td>JTc (msec)</td>
<td>300 ± 15</td>
<td>320 ± 20</td>
<td>310 ± 15</td>
<td>310 ± 15</td>
</tr>
<tr>
<td>TpTe (msec)</td>
<td>100 ± 10</td>
<td>120 ± 15</td>
<td>110 ± 10</td>
<td>110 ± 10</td>
</tr>
</tbody>
</table>

• Box Plot: ~30 min of Beat-to-Beat Lead II or VM Lead Data: JTp and TpTe

CONCLUSIONS

• We developed novel Stellar/TSE implants to record up to 5 ECG leads, including precordial leads (with the ability to calculate the 3 augmented leads online), along with arterial BP, body temperature, and activity.

• Our data demonstrated ability to accurately measure and determine compound-dependent differences in enhanced ECG intervals (JT and TpTe) to better understand proarrhythmia in telemetered animals.

• Results from combined dosing of "pure" ion channel blockers were in line with previously published clinical data, suggesting the translational value of the model.

• Results demonstrated ability to derive stable, reliable VM leads from freely moving, telemetered animals.

• Fewer outliers using VM leads for JTp and TpTe. Inclusion of V1 reduced JTp outliers to zero.

• Additional data analysis required to determine optimal leads/blends to cover VM lead.

• Dofetilide: Forward shift: QTc, JTc, and TpTe.

• Verapamil: PR prolongation. No effect on QRS with any test agent

• Mexiletine + dofetilide resulted in decreases in QTcV, JTpc, and TpTe

• Slight attenuation of JTpc in dofetilide + verapamil group vs dofetilide alone. No effect on TpTe

• Fewer outliers using VM leads for JTp and TpTe. Inclusion of V1 reduced JTp outliers to zero.

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