The Göttingen Minipig in Cardiovascular Safety Pharmacology

August 24, 2010
We will begin at 11:00AM
Webinar Logistics

- Event will be recorded and available for viewing

- Call in to listen via phone
  - select phone icon at bottom of attendee panel to view call information, (must enter Attendee ID).
  
  - Participant audio lines are muted

- 40 minute presentation; reserving 20 minutes for Q&A
  - Send your questions through the “Q&A” function, (expand to view). Questions will be answered at the end the presentation
The Göttingen Minipig in Cardiovascular Safety Pharmacology

Data for Reference Compounds

Michael Markert
Boehringer Ingelheim Pharma
Agenda

• Overview on the minipig and telemetry systems used

• Results using Dofetilide

• Results using Pimozide and Propranolol (BI data only)

• Summary
In a one-time surgical procedure the minipigs are instrumented with a Konigsberg ITS or DSI telemetry implant.

The detected parameters are:
- left ventricular pressure (ITS only)
- aortic blood pressure
- ECG
- temperature
Overview on study design

- Calming phase
- 1 h prevalues
- 7 h data recording
- 17 h data recording
- Application
- Feeding and blood sampling
LAB Research

- Implanted transmitter system recorded ECG, BP and temperature
- Data collected with Dataquest ART Acquisition, v. 2.3
- Analysed data using Physiostat ECG analysis v. 4.01, for the following timepoints:
  - -1, -0.5, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 20 hours post dosing
  - All ECG markers were visually inspected and replaced if necessary
Study results

Standard ECG parameters; results of mock studies in conscious minipigs

- PR: 125 ± 21 ms
- QRS: 56 ± 9 ms
- RR: 961 ± 172 ms
- QT: 330 ± 31 ms
Comparison dog-minipig QT-RR relationship
n=6, ~100,000 beats/animal
## Overview of compounds tested

<table>
<thead>
<tr>
<th></th>
<th>CIT</th>
<th>BI</th>
<th>Scantox</th>
<th>Ricerca</th>
<th>HLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dofetelide</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terfenadine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Cisapride</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>
Dofetilide, Effect on QT (BI data)
QT-RR regression

- 300 µg/kg
- 100 µg/kg
- 30 µg/kg
- control
Dofetilide, no effect on HR

![Graph showing heart rate (beats per min) over time for different doses of Dofetilide.](image)

- 0 ug/kg
- 30 ug/kg
- 100 ug/kg
- 300 ug/kg

- **Time (h)**: -1 Dosing 1 2 3 4 5 6 Feeding
- **Heart rate (beats per min)**: 0 10 20 30 40 50 60 70 80 90 100
Dofetilide, no effect on LVdP/dtmax
Dofetilide, ECG effects

- Significant QT increase (Fridericias correction) at 1, 1.5, 2 and 4 hours post dosing (females) in the high dose group

- Significant QT increase at 0.5, 2, 3 and 4 hours post dose (males) in the high dose group

- Treatment A – vehicle
- Treatment B – 30 µg/kg
- Treatment C – 100 µg/kg
- Treatment D – 300 µg/kg
PIMOZIDE (Parabolic, regression lines)

- 0.0mg/kg
- 1.0mg/kg
- 3.0mg/kg
- 10.0mg/kg

QTC (msec)

RR (sec)
Pimozide, effect on ECG morphology
AV block with 30mg/kg
Summary

• As expected from previous data the minipig needs often higher oral doses to achieve comparable (dog) Cmax exposure

• Pimozide and Dofetelide showed the expected increase in QT

• All companies detected a 35-50 ms QTc increase with 300 µg/kg Dofetelide and no effect on SAP, DAP, MAP, LVP*, LVdP/dtmax* up to 300 µg/kg

• Propranolol showed the expected beta-blocking effects:* A significant decrease in heart rate with all doses tested. The 20 mg/kg dose led to a maximum decrease to an average heart rate of 34 beats per minute

* BI data
Conclusion

• A cross-over study conducted with 6 minipigs was sensitive enough to detect a statistically significant QT prolongation when Dofetilide or Pimozide was administered in oral doses leading to clinically relevant plasma drug concentrations

• Propranolol showed the expected effects of a prototypical non-selective beta-adrenoceptor blocker and was shown to block sympathetic input to the heart with anticipated effects on heart rate and myocardial contractility. Indeed, propranolol in doses of 3, 10 and 20 mg/kg caused a substantial dose-dependent decrease in HR, myocardial contractility, and a shortening of the log-corrected QT interval

Göttingen Minipigs appear to be well suited as alternative non-rodent species to dogs and primates in pharmacological and toxicological telemetry studies