Respiratory safety pharmacology in rats, canines and non human primates: comparison of minimal detectable differences

Simon Authier1, Roy Forster1, Mylene Pouliot1, Alexis Ascah1 and Eric Troncy1
1CIToxLAB North America, 445 Armand Frappier, Laval, Quebec, Canada; 2Faculty of Veterinary Medicine, University of Montreal, 2200 Sicotte, St-Hyacinthe, QC, Canada

Introduction
Respiratory safety pharmacology can be included as part of repeat toxicology studies in rats, canines and non human primates (NHPs). Various parameters that impact sensitivity were evaluated by retrospective evaluation of historical control data from various species commonly used in toxicology.

Materials and methods
Respiratory data was obtained from head-out and whole body plethysmography in rats and with a pneumotachometer connected to a mask in canines. Respiratory data obtained with a helmet and bias flow or from freely moving animals were used for non human primates. The minimal detectable difference (MDD) was calculated for n=8 per group for respiratory rate (RR), tidal volume (TV) and minute ventilation (MV). Intervals of increasing durations from 10 seconds to 4 hours were used to assess the impact of super-intervals on data analysis. MDD calculations assumed an analysis at individual timepoints.

Discussion
Super-intervals were suggested as a strategy to increase sensitivity of cardiovascular data analysis (Sivarajah et al., 2010). The respiratory data is typically more variable than cardiovascular data partly due to behavioral modulations to breathing patterns. Our results confirm that super-intervals offer a strategy to improve respiratory data analysis in various species. The duration of data bins should be sufficiently long to increase sensitivity while providing adequate resolution to correlate results with PK profiles. MDDs for MV were lower in rats than large animal species (p<0.05) but theoretical statistical sensitivity estimations may differ from pharmacological responsiveness and the lower MDDs in rats may not translate into increased pharmacological sensitivity or clinical relevance (Legaspi et al., 2010). MDDs were lower in unrestrained non human primates while restrained rats presented comparable MDDs as freely moving animals. Nocturnal periods were associated with lower variability and consequently lower MDDs.

Results

Circadian variability of tidal volume in freely moving cynomolgus monkeys (n=8)

<table>
<thead>
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<th>Time of the day</th>
<th>0%</th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>80%</th>
<th>100%</th>
</tr>
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<tbody>
<tr>
<td>Night</td>
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<td>30%</td>
<td>45%</td>
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</tr>
<tr>
<td>Day</td>
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<td>20%</td>
<td>30%</td>
<td>40%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Conclusion
Super-intervals were useful to decrease minimal detectable differences with respiratory data. The rat presented lower minimal detectable differences for all evaluated parameters.

References