Pharmacokinetics of tildipirosin in bovine plasma, lung tissue and bronchial fluid (from live, non-anesthetized cattle)

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Background:
The novel 16-membered semi-synthetic macrolide Tildipirosin (Zuprevo® 180 mg/mL solution for injection for cattle, MSD Animal Health) has recently been approved for treatment and prevention of bovine respiratory disease (BRD) associated with M. haemolytica, P. multocida and H. somni in the EU.

Objectives:
Pharmacokinetic (PK) studies were performed to assess
- Absolute bioavailability.
- Drug concentrations in plasma, lung tissue and bronchial fluid collected in vivo.

Materials and Methods:
Experimental design (see Table 1 for details on treatment groups):
Up to 14 cattle per group were administered tildipirosin (TIP) once either by subcutaneous (SC) or intravenous (IV) injection at the recommended clinical dose of 4 mg/kg body weight (BW) or at 2 or 6 mg TIP/kg BW.

Sampling (see Table 1):
Samples of plasma, bronchial fluid from live, non-anesthetized cattle and lung tissue were collected:
- Plasma: before and 0.5, 1, 2, 4, 8, 10 h and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14 and 21 days after administration (studies A and C); additional samples were obtained at 5, 15 and 90 min after administration (study C).
- Bronchial fluid: before and 4, 10 h and 1, 3, 4, 5, 10, 14 and 21 days after administration (study A).
- Lung tissue: from 2 animals each at days 5, 10 and 14 (study A) and from 4 animals each at 4, 10 h and at days 1, 3, 18, 21 and 28 (study B).

Testing:
TIP concentrations were determined by HPLC-MS/MS and used for non-compartmental PK analysis (WinNonlin®, Pharsight Corp.).

The following PK parameters were determined:
- Concentration (Cmax) (maximum observed concentration in plasma)
- Tmax (time to reach maximum observed concentration in plasma)
- AUC0-∞ (area under concentration- vs. - time curve from time 0 to the last sampling time associated with a quantifiable drug concentration)
- AUC0-t (area under concentration- vs. - time curve from time zero extrapolated to infinity (predicted))
- T½ (terminal half life)
- MRT0-∞ (mean residence time from the time of dosing to the time of last quantifiable concentration)
- CLtot (clearance)
- V of (volume distribution based on the terminal phase)
- F (absolute bioavailability) = [(mean AUC0-∞ (SC)/mean AUC0-∞ (IV)) x (dose (IV)/dose (SC))] x 100

Results:
- After administration of the recommended dose (4 mg/kg BW SC) mean maximum plasma concentration (Cmax) was 0.7 and 0.6 µg/mL in study groups A2 and C1 (see Table 2) and mean time to reach Cmax (Tmax) was 41 and 23 min (see Table 2) (Note: the difference is caused by the difference in sampling time points).
- The mean terminal half life (T½) was ~9 days (see Table 2).
- The mean residence time from the time of dosing to the time of last quantifiable concentration (MRT0-∞) was ~6 days (see Table 2).
- Mean Cmax and area under the concentration versus time curve (AUC) increased dose dependently (Figure 1).
- Absolute bioavailability was 78.9% (Table 2).
- The volume of distribution based on the terminal phase (Vf) was 49.4 L/kg and the clearance was 144 mL/h/kg (Table 2).
- The time-concentration profiles of TIP in bronchial fluid and lung far exceeded that in blood plasma (Figure 2).
- In lung, TIP concentrations reached 9.2 µg/g at 4 h, peaked at 14.8 µg/g at day 1 and slowly declined to 2.0 µg/g at day 28 (Figure 2).
- In bronchial fluid, TIP levels reached 1.5 and 3.0 µg/g at 4 h and 10 h, maintained a plateau of 3.5 µg/g between day 1 and 3 and slowly declined to 1.0 at day 21 (Figure 2).

Conclusions:
Tildipirosin is rapidly and extensively distributed to the respiratory tract followed by slow elimination.

Table 1: Treatment groups.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Number of animals</th>
<th>Dose</th>
<th>Route</th>
<th>Samples taken</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bronchial fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lung tissue</td>
</tr>
<tr>
<td>Study A</td>
<td>A1</td>
<td>5</td>
<td>2</td>
<td>SC</td>
<td>X</td>
</tr>
<tr>
<td>Study A</td>
<td>A2</td>
<td>14</td>
<td>4</td>
<td>SC</td>
<td>X</td>
</tr>
<tr>
<td>Study A</td>
<td>A3</td>
<td>5</td>
<td>6</td>
<td>SC</td>
<td>X</td>
</tr>
<tr>
<td>Study B</td>
<td>B1-B7</td>
<td>28</td>
<td>4</td>
<td>SC</td>
<td>-</td>
</tr>
<tr>
<td>Study C</td>
<td>C1</td>
<td>6</td>
<td>4</td>
<td>SC</td>
<td>-</td>
</tr>
<tr>
<td>Study C</td>
<td>C2</td>
<td>2</td>
<td>6</td>
<td>IV</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2: Plasma PK parameters after single SC administration of 180 mg/mL tildipirosin solution for injection at the recommended dose of 4 mg/kg body weight (groups A2 and C1) and single IV administration at 2 mg/kg body weight (group C2).

Parameter (unit) | Group A2 | Group C1 | Group C2 |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.711 ± 0.274</td>
<td>0.639 ± 0.197</td>
<td>n.a.</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>41.4 ± 15.6</td>
<td>22.8 ± 7.8</td>
<td>n.a.</td>
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<tr>
<td>T½ (d)</td>
<td>8.8 ± 2.21</td>
<td>8.5 ± 0.58</td>
<td>9.9 ± 1.92</td>
</tr>
<tr>
<td>MRT0-∞ (d)</td>
<td>6.3 ± 0.54</td>
<td>6.0 ± 0.17</td>
<td>6.3 ± 0.92</td>
</tr>
<tr>
<td>CLtot (mL/h/kg)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>144 ± 7</td>
</tr>
<tr>
<td>Vf (L/kg)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>F (%)</td>
<td>n.a.</td>
<td>78.9</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Figure 1: Mean Cmax and area under the concentration- vs. - time curve (AUC) after single SC administration of 180 mg/mL tildipirosin solution for injection at doses of 2, 4 and 6 mg/kg body weight.

Figure 2: Mean ± SD tildipirosin concentration in bovine plasma (µg/mL), lung tissue and bronchial fluid (µg/g) from live, non-anesthetized cattle following single SC administration at a dose of 4 mg/kg body weight (studies A, B).