Influence of mycotoxin binders on the oral bioavailability of doxycycline in pigs

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www.mytox.be

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Introduction: Mycotoxin binders

Mycotoxin detoxifiers

Mycotoxin binders

Clay based

Yeast based

Mycotoxin modifiers

Others, e.g. cholestyramine
Introduction: Mycotoxin binders

- Feed additive: as mycotoxin binder
  Recommended level: 1 – 2 g/kg (0.1% - 0.2%)

- Feed additive: for technological purposes
  Maximally 20 g bentonite/kg feed (2%)

(Text with EEA relevance)

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Introduction: Doxycycline (DOX)

- Tetracycline antibiotic
- *Mycoplasma spp.*, *Actinobacillus pleuropneumoniae*, *Bordetella bronchiseptica*, etc.
- Oral bioavailability is lower in fed animals

(ESVAC, 2016)
Aims

Mycotoxin binders: feed additives

Antimicrobials (doxycycline): Oral administration via feed/drinking water

Non-specific interaction in the GIT?

Interaction depends on
- inclusion rate?
- prandial status?
Experiment 1: Study design

**Fasted** animals, single oral bolus:
- Daily dose of mycotoxin binder (≈0.2% inclusion rate)
- DOX (10 mg/kg BW)

**Control**  
**Clay 1**  
**Clay 2**  
**Clay 3**  
**Yeast 1**

Blood sampling at different time points after DOX administration  
LC-MS/MS analysis of DOX in plasma  
Comparing PK
### Experiment 1: Results

\[ Relative \, F(\%) = \frac{AUC \, test \, group}{AUC \, control} \times 100 \]

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Control</th>
<th>Clay 1</th>
<th>Clay 2</th>
<th>Clay 3</th>
<th>Yeast 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>( AUC_{0-12h} ) (h·µg/mL)</td>
<td>9.60 ± 3.49</td>
<td>12.29 ± 4.57</td>
<td>9.73 ± 2.35</td>
<td>6.37 ± 2.63</td>
<td>10.72 ± 5.59</td>
</tr>
<tr>
<td>( AUC_{0-inf} ) (h·µg/mL)</td>
<td>10.56 ± 3.97</td>
<td>12.90 ± 4.84</td>
<td>10.43 ± 2.42</td>
<td>7.54 ± 2.67</td>
<td>11.78 ± 6.04</td>
</tr>
<tr>
<td><strong>Relative F (%)</strong></td>
<td>100.00 ± 37.61</td>
<td>122.31 ± 45.87</td>
<td>98.91 ± 22.95</td>
<td><strong>71.50 ± 25.34</strong></td>
<td>111.69 ± 57.28</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>2.00 ± 1.10</td>
<td>2.83 ± 1.47</td>
<td>2.50 ± 1.64</td>
<td>2.17 ± 1.47</td>
<td>2.50 ± 1.22</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (µg/mL)</td>
<td>2.01 ± 0.91</td>
<td>2.46 ± 0.90</td>
<td>2.12 ± 0.77</td>
<td>1.31 ± 0.75</td>
<td>1.93 ± 1.06</td>
</tr>
<tr>
<td>( k_{el} ) (1/h)</td>
<td>0.23 ± 0.08</td>
<td>0.29 ± 0.05</td>
<td>0.22 ± 0.04</td>
<td>0.21 ± 0.13</td>
<td>0.23 ± 0.06</td>
</tr>
<tr>
<td>( T_{1/2el} ) (h)</td>
<td>4.83 ± 1.74</td>
<td>3.57 ± 0.52</td>
<td>4.69 ± 0.87</td>
<td>6.59 ± 3.95</td>
<td>4.60 ± 1.11</td>
</tr>
<tr>
<td>( Vd/F ) (L/kg)</td>
<td>4.77 ± 1.35</td>
<td>3.07 ± 1.12</td>
<td>4.66 ± 1.14</td>
<td>9.26 ± 5.81</td>
<td>5.36 ± 3.92</td>
</tr>
<tr>
<td>( Cl/F ) (L/h/kg)</td>
<td>1.09 ± 0.46</td>
<td>0.88 ± 0.33</td>
<td>1.00 ± 0.23</td>
<td>1.45 ± 0.43</td>
<td>1.15 ± 0.76</td>
</tr>
</tbody>
</table>
Experiment 2: Study design

**Fasted** animals, single oral bolus:
- Daily dosis of mycotoxin binder (*~1% inclusion rate*)
- DOX (10 mg/kg BW)

Control  Clay 1  Clay 3

Blood sampling at different time points after DOX administration
LC-MS/MS analysis of DOX in plasma
Comparing PK
## Experiment 2: Results

### Treatment group: Control, Clay 1, Clay 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Clay 1</th>
<th>Clay 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-12h}$ (h·µg/mL)</td>
<td>9.60 ± 3.49</td>
<td>2.26 ± 2.16*</td>
<td>1.49 ± 0.94†</td>
</tr>
<tr>
<td>AUC$_{0-inf}$ (h·µg/mL)</td>
<td>10.56 ± 3.97</td>
<td>2.28 ± 2.55*</td>
<td>2.07 ± 1.02*</td>
</tr>
<tr>
<td>Relative F (%)</td>
<td>100.00 ± 37.61</td>
<td>21.62 ± 24.14*</td>
<td>19.67 ± 9.64*</td>
</tr>
<tr>
<td>T$_{max}$ (h)</td>
<td>2.00 ± 1.10</td>
<td>4.50 ± 2.07</td>
<td>4.50 ± 3.83</td>
</tr>
<tr>
<td>C$_{max}$ (µg/mL)</td>
<td>2.01 ± 0.91</td>
<td>0.45 ± 0.40*</td>
<td>0.32 ± 0.21*</td>
</tr>
<tr>
<td>k$_{el}$ (1/h)</td>
<td>0.23 ± 0.08</td>
<td>0.33 ± 0.16</td>
<td>0.15 ± 0.06</td>
</tr>
<tr>
<td>T$_{1/2el}$ (h)</td>
<td>4.83 ± 1.74</td>
<td>3.44 ± 1.19</td>
<td>7.44 ± 2.44</td>
</tr>
<tr>
<td>Vd/F (L/kg)</td>
<td>4.77 ± 1.35</td>
<td>26.77 ± 18.28</td>
<td>45.46 ± 32.81‡</td>
</tr>
<tr>
<td>Cl/F (L/h/kg)</td>
<td>1.09 ± 0.46</td>
<td>8.16 ± 4.80‡</td>
<td>6.11 ± 3.51‡</td>
</tr>
</tbody>
</table>
Experiment 3: Study design

Continuous administration in the feed:
- Mycotoxin binder (0.2% inclusion rate)
- DOX: 270 mg/kg feed (~10 mg/kg BW)

Blood sampling at different time points after DOX administration
LC-MS/MS analysis of DOX in plasma
Comparing PK
## Experiment 3: Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Clay 1</th>
<th>Clay 2</th>
<th>Clay 3</th>
<th>Yeast 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{ss}$ (ng/mL)</td>
<td>143.02 ± 29.48</td>
<td>144.46 ± 24.32</td>
<td>121.50 ± 28.53</td>
<td>127.86 ± 15.89</td>
<td>137.23 ± 27.37</td>
</tr>
<tr>
<td>AUC$_{0-58h}$ (h·µg/mL)</td>
<td>7.34 ± 1.35</td>
<td>7.18 ± 1.22</td>
<td>6.05 ± 1.28</td>
<td>6.10 ± 1.04</td>
<td>6.76 ± 1.60</td>
</tr>
<tr>
<td>Relative F (%)</td>
<td>100.00 ± 24.21</td>
<td>97.82 ± 21.87</td>
<td>82.43 ± 18.95</td>
<td>83.11 ± 14.54</td>
<td>92.10 ± 13.28</td>
</tr>
</tbody>
</table>
**Discussion & Conclusions**

- Interaction possible at high dose, in fasted animals
- No interactions observed at low dose
- Confirms *in vitro* results using feed containing buffered matrix (Poster 17)
- Bolus model
- EFSA (2010)
  - Highest recommended dose
  - Steady state design: veterinary medicinal product in feed, 5 days sampling
- Further information
  - De Mil et al.

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*STIFIC OPINION*

Draft guidelines for the assessment of additives for reduction of the contamination of feed by mycotoxins.

EFSA Journal 2010; 8(7):1693

European Food Safety Authority (EFSA), Parma, Italy