Ionophore toxicity in poultry

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Outline

- Anti-coccidials classification
- Ionophores
- Mode of action
- Ionophore toxicity
- Possible causes for ionophore toxicity
- Clinical signs
- Gross pathology and histopathology
- Diagnosis and treatment
- Take home message
## Anti-coccidials classification

### Ionophores

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Active ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coban</td>
<td>Monensin</td>
</tr>
<tr>
<td>Monteban</td>
<td>Narasin</td>
</tr>
<tr>
<td>BioCox 120G</td>
<td>Salinomycin</td>
</tr>
<tr>
<td>Salinomycin 60</td>
<td></td>
</tr>
<tr>
<td>Sacox 120</td>
<td></td>
</tr>
<tr>
<td>Coxistac</td>
<td></td>
</tr>
<tr>
<td>Avatec</td>
<td>Lasalocid</td>
</tr>
<tr>
<td>Cygro</td>
<td>Maduramicin</td>
</tr>
</tbody>
</table>

### Chemical drugs

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Active ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprol</td>
<td>Amprolium</td>
</tr>
<tr>
<td>Nicarbaz</td>
<td>Nicarbazin</td>
</tr>
<tr>
<td>Zoamix</td>
<td>Zoalene</td>
</tr>
<tr>
<td>Coyden</td>
<td>Clopidol</td>
</tr>
<tr>
<td>Robenz</td>
<td>Robenidine</td>
</tr>
<tr>
<td>Deccoxx</td>
<td>Decoquinate</td>
</tr>
<tr>
<td>Clinacox</td>
<td>Diclazuril</td>
</tr>
</tbody>
</table>

*Elanco poultry anticoccidial reference guide*
Ionophores

- Ionophores are polyether compounds used in control of coccidiosis

- Fermentation products of *Streptomyces* and other fungi species

- They form lipid soluble complexes with cations & facilitate specific ion transport across biological membranes
Ionophore classification

Classification – based on affinity for cations

- **Monovalent ionophores**
  - Tend to combine with Na\(^+\) and K\(^+\)
  - Eg – monensin, narasin, salinomycin
  - Monensin – choice of product for poultry
    - Broad-spectrum activity against coccidia
    - Slow development of drug resistance

- **Divalent ionophores**
  - Combines with Na\(^+\), K\(^+\) as well as with Ca\(^{2+}\), Mg\(^{2+}\)
  - Eg- lasalocid

+ & ++
Mode of action

- Most ionophores act against 1\textsuperscript{st} & 2\textsuperscript{nd} asexual cycle of coccidia
  - Act on sporozoites and merozoites
- Some act against sexual stages of the life cycle

(MERCK Animal Health)

Chapman, 2010
Activity of anticoccidials in coccidial life cycle
Mode of action

- Ionophores form lipid soluble complexes with cations (Na\(^+\), K\(^+\), Ca\(^{2+}\) & Mg\(^{2+}\)) & interfere with normal transport of cations across surface membranes of parasite / modify permeability
- Alteration of normal concentration gradients of ions
Mode of action

- Increased intracellular Na\(^+\) inhibits mitochondrial functions

- Excessive increase of intracellular Ca\(^{2+}\) exceeds the ability of mitochondria to effectively sequester Ca\(^{2+}\) & it causes membrane damage, cell swelling and bursting
## Recommended Dosage

<table>
<thead>
<tr>
<th>Ionophore</th>
<th>Broiler Chickens Dosage (ppm)</th>
<th>Turkey Dosage (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monensin</td>
<td>100</td>
<td>100 (up to 12 wks)</td>
</tr>
<tr>
<td>Narasin</td>
<td>70</td>
<td>Toxic</td>
</tr>
<tr>
<td>Lasalocid</td>
<td>105</td>
<td>100 (up to 14 wks female /16 wks male)</td>
</tr>
<tr>
<td>Salinomycin</td>
<td>60</td>
<td>Toxic</td>
</tr>
<tr>
<td>Maduramycin</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
## Narrow safety margin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Optimal dose (ppm)</th>
<th>Lowest level of toxicity (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monensin</td>
<td>100-125</td>
<td>121-150</td>
</tr>
<tr>
<td>Narasin</td>
<td>60-80</td>
<td>80-100</td>
</tr>
<tr>
<td>Lasalocid</td>
<td>75-125</td>
<td>125-150</td>
</tr>
<tr>
<td>Salinomycin</td>
<td>60-75</td>
<td>100</td>
</tr>
</tbody>
</table>

Dowling, 1992
Ionophore toxicity in poultry

- Normal cell ionic gradient is maintained by transport complexes – $\text{Na}^+\text{K}^+\text{ATPase} / \text{Ca}^{2+}\text{Mg}^{2+}\text{ATPase} / \text{Na}^+\text{Ca}^{2+}$ counter transport system

- Ionophore toxicity – disrupt normal ionic gradients of cells
  - Excess $\text{Ca}^{2+}$ overload causes mitochondrial damage, and it will leads to reduced cellular energy and muscle necrosis
  - Less $\text{Ca}^{2+}$ for muscle contraction
  - Deplete intracellular ATP levels as higher expenditure of ATP to maintain normal ionic balance inside cells
Possible causes for ionophore toxicity

- Accidental overdose
- Uneven distribution of drug in feed
- Contamination of feed
- Some dietary interactions – protein and fat source/level, minerals
- Dehydration (turkeys)
- Interactions with other drugs
## Compatibility with other drugs

<table>
<thead>
<tr>
<th>Ionophore</th>
<th>Virginiamycin</th>
<th>Bacitracin</th>
<th>Bacitracin* (7 days)</th>
<th>Zn Bacitracin</th>
<th>Flavomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monensin</strong></td>
<td>11</td>
<td>55</td>
<td>110</td>
<td><strong>X</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Narasin</strong></td>
<td>11</td>
<td>55</td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
</tr>
<tr>
<td><strong>Lasalocid</strong></td>
<td>11</td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
</tr>
<tr>
<td><strong>Salinomycin</strong></td>
<td>11</td>
<td>55</td>
<td>110</td>
<td><strong>X</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Maduramycin</strong></td>
<td>11</td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
<td>4.4</td>
<td>2</td>
</tr>
</tbody>
</table>

*Elanco poultry anticoccidial reference guide*
Interaction with other drugs

- Check the compatibility with other drugs
  - Drug label
  - Veterinarian

- Toxicity cases have reported
  - Monensin + sulphaquinoxaline/sulphamethazine/sulphadimethoxine
  - Monensin/narasin/salinomycin + erythromycin

Dowling, 1992
Effect of fat level & source

- Diet containing monensin (150 ppm)
  - Significantly decrease feed intake & weight gain

- Fat (Soybean oil/SO) 3 vs. 6%
  - Increase weight gain, FI and feed efficiency
  - Fat affect on drug metabolizing enzymes
  - High energy in fat alleviate growth depression

- Effect of fat source (SO vs. beef tallow)
  - Increasing SO level alleviate growth depressing effect compare to tallow
  - Unsaturated fat increase the activity of drug metabolizing enzymes

Bartov, 1987
Effect of protein source

- Monensin (100 & 120 ppm) containing corn-SBM diet
  - No significant depression of growth and feed utilization

- Medium & high animal protein (fish meal) diet (13 & 24.5%)
  - Significant reduction of performance compare to SBM
  - Less potassium level in fish meal compare to SBM

Bartov & Jensen, 1980
Effect of protein level

- Monensin supplementation (140 ppm) - corn-SBM diet
  - Reduced growth rate 18 & 10% in chicks fed CP 20 & 24%
  - Increasing CP to 28% further alleviated the adverse effect of monensin on weight gain

Welch, 1986
Effect of dietary potassium

- Monensin (140 & 160 ppm) in diet
- Fish meal or/and poultry by-product vs. SBM
  - Growth depression with animal protein compared to SBM
  - Addition of K (0 vs. 0.3%) into diet counteracted the growth depression effect
  - K improves electrolyte balance
Clinical signs

- Incoordination
- Leg weakness
- Abnormal gait / toe walking
- Diarrhoea
- Ruffled feathers
- Reduced feed intake
- weight depression
- Decreased egg production – broiler breeders
- Paralysis and death
Salinomycin toxicity - turkeys

Sternal recumbency with neck and limbs outstretched
Salinomycin toxicity - turkeys
Clinical signs

Dyspnea – difficulty in breathing
Gross pathology

- Emaciation / dehydration
- Generalized congestion
- Myocardial enlargement
Gross pathology

- Emaciation /dehydration
- Generalized congestion
- Myocardial enlargement
- Hydropericardium
Gross pathology

- Emaciation /dehydration
- Generalized congestion
- Myocardial enlargement
- Hydropericardium
- Ascites
Gross pathology

- Emaciation/dehydration
- Generalized congestion
- Myocardial enlargement
- Hydropericardium
- Ascites
- Egg peritonitis
Gross pathology

- Emaciation /dehydration
- Generalized congestion
- Myocardial enlargement
- Hydropericardium
- Ascites
- Egg peritonitis
- Spleen atrophy
Gross pathology

- Emaciation/dehydration
- Generalized congestion
- Myocardial enlargement
- Hydropericardium
- Ascites
- Egg peritonitis
- Spleen atrophy
- Liver degeneration
- Enlarged kidneys
Salinomycin toxicosis - turkeys

(A) Growth retardation in 35 days old poulns, (B) Pica, (C) Spleen atrophy

Koutoulis, 2013
Normal histology of muscle tissue

Inflammatory & degenerative lesions of muscle tissue
Differential diagnosis

- Nutritional (focal) myopathy – vitamin E & selenium deficiency
- Sodium chloride (salt) toxicity
- Botulism
- Myopathic mycotoxins
- Newcastle disease
- Marek’s disease
Diagnosis

- Recovery of remaining birds in the affected flock when removed from the feed & presence of clinical signs
- Gross pathology lesions are not pathognomonic
- Presence of histological myopathies
- Increased concentrations of ionophores in feed
Treatment

- No known antidote or treatment for ionophore toxicity
- When suspected, immediately change the feed to another ration until complete the diagnosis
Take home message

- Use the exact dose of ionophores / species relevance
- Prevent contamination of feed
- Check drug compatibility when using ionophores with other drugs / consult veterinarians
- Immediately change the feed to another ration if ionophore toxicity is suspected in a flock
Acknowledgements

- Dr. Jenny Fricke
- Dr. Hank Classen
- Tennille Knezacek
Questions?

THANK YOU