The Changing Face of Rodenticides
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Urbana, IL

Rodenticides
- Commonly encountered
- Accurate identification required
  - Each class unique
- Color and formulation not unique
  - Baits come in blocks, pellets and granules
  - Blue, green, red or tan

- Anticoagulants
- Bromethalin
- Cholecalciferol
- Strychnine
- Zinc phosphide
Glue Traps

- No poisons
  - Unless added by the owner
- Product kills by starvation or suffocation

Glue traps

- Any oily substance (olive oil, mayonnaise, peanut butter, mineral oil, vegetable oil) can help remove non-water soluble compounds
  - Rub a small amount into the affected area
  - Keep rubbing until substance breaks down into “gummy balls”
  - Wash with liquid dish washing detergent to remove the oily substance

Rodenticide changes

- EPA rodenticide regulations
  - Children
  - Wildlife
    - Direct toxicosis
    - Relay toxicosis

Red-tailed hawk poisoned by rodenticides
Photo: AmericasASP
New Rules: consumer products

♦ Contain < one pound bait
  ♦ Cannot contain: brodifacoum, difethialone, bromadiolone, difenacoum
    Can use first-generation anticoagulants or non-anticoagulants
  ♦ No loose baits (pellets), must include a bait station
    ♦ Can include bait refills

New Rules: professional products

♦ Bait stations
♦ First generation anticoagulant or non-anticoagulant baits
  ♦ > four pounds
♦ Second generation anticoagulant baits
  ♦ > 16 pounds bait when labeled for use above ground outdoors
  ♦ > eight pounds of poison bait when labeled for use around agricultural buildings

New concerns

♦ Will other types of baits without antidotes become more popular?
  ♦ Bromethalin
  ♦ Cholecalciferol
  ♦ Strychnine
  ♦ Zinc phosphide
### Anticoagulants - Mechanism of Action

- Stops production of clotting factors
- Inhibit vitamin K 1,2,3-epoxide reductase
- Prevents vitamin K recycling
- Affected factors
  - II, VII, IX, and X
  - extrinsic, intrinsic and common coagulation pathways

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### Half-life in Dogs

- Vitamin K-dependent factors: II, VII, IX, & X

- Platelets: 6.2 hours
- Intrinsic: 10.5 hours
- Extrinsic: 15.9 hours
- Common: 41 hours
- APTT: 16.5 hours
- DSPT: 8.1 hours
- Fibrin: 19.2 hours

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### Activity Ingredient

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
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<td>Difenacoum</td>
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<td>6</td>
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<td>4</td>
<td>6</td>
<td>7</td>
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<td>Difethialone</td>
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<td>Bromethalin</td>
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<td>2112</td>
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<td>Cholecalciferol</td>
<td>59</td>
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<td>20</td>
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<td>21</td>
<td>703</td>
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<td>Zinc Phosphide</td>
<td>207</td>
<td>192</td>
<td>199</td>
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<td>230</td>
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<td>7519</td>
<td>7997</td>
<td>9882</td>
<td>12209</td>
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Anticoagulant Rodenticides

First generation
- Short acting
- Developed prior to 1971
- Dicoumarol, warfarin, pindone, chlorphacinone, valone
- Rapid excretion – multiple doses required

Second generation (superwarfarins)
- Long acting
- Developed in 1970’s – 1980’s+
- Brodifacoum, bromadiolone, aplanochlor, difethialone, difenacoum
- Longer half-life – one feeding sufficient

Kinetics
- Generally 3-7 days before clinical signs are seen
  - Factor VII has shortest half-life (6.2 hours)
- Duration of clinical signs:
  - warfarin - 14 days
  - bromadiolone - 21 days
  - brodifacoum - 30 days (stored in the liver)
Clinical Signs

- Coagulopathies develop as vitamin K dependent clotting factors are depleted

- Initially, signs are vague:
  - lethargy
  - exercise intolerance
  - +/- anorexia

Clinical Signs

- As signs progress:
  - weakness
  - frank hemorrhage
  - dyspnea
  - bruising
  - lameness
  - seizures
  - death

Anticoagulant rodenticides

- Diagnosis
  - Analysis of liver – post mortem
  - Monitor PT and/or PIVKA (Protein Induced by Vitamin K Absence)
    - Baseline, 48, and 72 hours
    - PIVKA may become abnormal at 24 hours
    - Consider previous injections of Vitamin K₃
  - In horses, PTT may go up first by 24 hours
    - PT goes up by 48 hours
**Decontaminate**

- **Warfarin**
  - Decontaminate at 0.5 mg/kg
- **Second generation**
  - Decontaminate at 0.02 mg/kg
- **Emesis**
  - if less than 4 hours following ingestion
    - grain-baits stay in stomach longer
- **Activated charcoal**
  - benefit of repeat doses not proven

**K1 or not K1, that is the question**

- Witnessed or just some evidence
  - Chewed package
  - Green stools
- Age of animal - young are more sensitive
- Previous health state
  - Concurrent medications
- PT at baseline, 48 hours, 72 hour

**Treatment**

- **Vitamin K1**
  - 2.5-5 mg/kg/day divided BID-TID PO, IM, SQ (difference in absorption is only minutes)
  - 6-12 hours for new clotting factors to be synthesized
  - give with fatty meal to increase absorption
Treatment

- Small animals
  - Injectable product may be given orally
    Useful for treating rabbits, rodents

- Monitor PT 48 hours after last dose of Vitamin K1

Treatment

- Emergency needs for clotting factors (whole blood transfusion, fresh plasma, fresh frozen plasma)
- Oxygen
- Restrict exercise/cage rest

Anticoagulant rodenticides

- Cross placenta, excreted into milk
Primary and Secondary Toxicity

- Primary toxicity to all mammals is high
- Poisoned rodents have killed avian and mammalian secondary consumers

Bromethalin

- Neurotoxin - NOT an anticoagulant!
  - Usually contains 0.01% bromethalin
  - 0.75 oz place packs, 0.5 oz bars, pellets
- Assault®, Vengeance®, Sudden Death®, Fastrac®

Mechanism of Action

- Oxidative phosphorylation uncoupled
  - ATP production
  - Loss of Fluid Pumps
  - Edema of Myelin Sheaths
Toxicity

- Minimum toxic dose
  - Literature 1.67 mg/kg
  - APCC 0.9 mg/kg
- Converted to desmethylbromethalin
  - Several times more toxic than bromethalin
- Half life (dog) = 5.6 days
  - Enterohepatic recirculation

<table>
<thead>
<tr>
<th>Animal</th>
<th>LD50 mg/kg</th>
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<tbody>
<tr>
<td>Norway Rat</td>
<td>2</td>
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<tr>
<td>Mouse</td>
<td>5</td>
</tr>
<tr>
<td>Dog</td>
<td>4.7</td>
</tr>
<tr>
<td>Cat</td>
<td>1.8</td>
</tr>
<tr>
<td>Monkey</td>
<td>5</td>
</tr>
<tr>
<td>Rabbit</td>
<td>13</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Bromethalin – Clinical Signs

- Acute syndrome (doses at or above LD)
  - Signs appear about 10 hours post ingestion
  - Mortality rate ~100%
  - Agitation, depression, hind limb paresis, tremors, seizures, death

Bromethalin – Clinical Signs

- Chronic syndrome
  - Doses below the LD
  - Signs may occur 24-86 hours post exposure
  - Signs may last up to 12 days
    - may fully recover or may have permanent impairment
  - Tremors, depression, ataxia, rear limb paresis, vomiting, recumbency
Treatment

- DECONTAMINATION
- DECONTAMINATION
- DECONTAMINATION
- Emesis
- Activated charcoal (repeated)
- If clinical signs are present, try to decrease cerebral edema
  - Dexamethasone
  - Mannitol
  - Furosemide

Decontamination - Dog

<table>
<thead>
<tr>
<th>Time since exposure</th>
<th>Dose Ingested (mg/kg)</th>
<th>Action Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 hours</td>
<td>0.1 - 0.49</td>
<td>Emesis or one dose of charcoal</td>
</tr>
<tr>
<td>&gt; 4 hours</td>
<td>0.1 - 0.49</td>
<td>One dose of charcoal</td>
</tr>
<tr>
<td>&lt; 4 hours</td>
<td>0.5 - 0.75</td>
<td>Emesis and three doses of charcoal</td>
</tr>
<tr>
<td>&gt; 4 hours</td>
<td>0.5 - 0.75</td>
<td>Three doses of charcoal</td>
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<tr>
<td>&lt; 4 hours</td>
<td>&gt; 0.75</td>
<td>Emesis and three doses of charcoal per day for 48 hours</td>
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<tr>
<td>&gt; 4 hours</td>
<td>&gt; 0.75</td>
<td>Three doses of charcoal per day for 48 hours</td>
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Decontamination - Cat

<table>
<thead>
<tr>
<th>Time since exposure</th>
<th>Dose Ingested (mg/kg)</th>
<th>Action Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 hours</td>
<td>0.05 - 0.1</td>
<td>Emesis or one dose of charcoal</td>
</tr>
<tr>
<td>&gt; 4 hours</td>
<td>0.05 - 0.1</td>
<td>One dose of charcoal</td>
</tr>
<tr>
<td>&lt; 4 hours</td>
<td>0.1 - 0.3</td>
<td>Emesis and three doses of charcoal</td>
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<tr>
<td>&gt; 4 hours</td>
<td>0.1 - 0.3</td>
<td>Three doses of charcoal</td>
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<tr>
<td>&lt; 4 hours</td>
<td>&gt; 0.3</td>
<td>Emesis and three doses of charcoal per day for 48 hours</td>
</tr>
<tr>
<td>&gt; 4 hours</td>
<td>&gt; 0.3</td>
<td>Three doses of charcoal per day for 48 hours</td>
</tr>
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</table>
Prognosis

- Prognosis varies with severity of presenting signs
  - Asymptomatic or mild depression, ataxia = good prognosis, recovery in 1-2 weeks
  - Severe neurologic signs (coma, paralysis) = poor prognosis

Why talk about cholecalciferol?

- 2017
  - Only 21 cases
- 2018
  - 703 cases
- Plus another 2300 supplement cases
Cholecalciferol (Vitamin D) Rodenticides

- Mouse-B-Gon®, Rat-B-Gon®, Quintox®, Rampage®, True Grit®
- Marked increase in serum calcium and phosphorus
- Soft tissue mineralization
- Renal failure

Mechanism of Action

**Cholecalciferol**

- Liver
- Calcifediol
- Kidney
- Calcitriol
  - ↑ intestinal absorption of Ca
  - ↑ renal tubular reabsorption of Ca
  - Stimulates bone resorption of Ca

**Mechanism of Action**

- High Ca and P → soft tissue mineralization
Cholecalciferol Radiography

Toxicity
- LD50 in dogs (technical product)
  - 88 mg/kg in the dog
- Minimum toxic dose in dogs (bait)
  - 0.5 mg/kg
  - Decontaminate at 0.1mg/kg
- Juvenile animals and animals with renal disease may be more sensitive

Cholecalciferol - Kinetics
- Rapid absorption
- Highly lipophilic
- Enterohepatic recycling
Cholecalciferol - clinical signs

- Early (12-36 h)
  - Weakness, lethargy, anorexia
  - Polyuria and polydipsia
  - Vomiting, often with blood
  - Increased P (12 h), Ca and azotemia (24 h)
- Later signs
  - Oliguria and anuria
  - Calcification of renal tubules and other highly vascular tissues and vessel walls

Decontamination

- Emesis if ingestion was < 4 hours ago
- Activated charcoal with cathartic
- Cholestyramine
  - 300 mg/kg PO TID for 4 d
- Baseline (< 8 hours post-exposure) Ca, P, BUN, creatinine
  - Repeat q 12-24 hours, for 4 days
  - Goal is Ca x P < 60

Puppies

- Have normally “high” phosphorus compared to adults
- May persist up to year in large breed dogs
- Ca X P is normally > 70-80
**Treatment**
- If $\text{Ca (mg/dl)} \times \text{P (mg/dl)} > 60$
  - Soft tissue mineralization may occur
  - Guideline only – monitor trends
- Diurese with 0.9% NaCl
  - Avoid calcium containing fluids
- Furosemide
- Prednisolone
- Phosphate binder
- Low Ca diet
  - k/d, u/d, s/d, pasta and lean ground beef

**If Ca x P still rising...**
- Bisphosphonates, treats hypercalcemia in people
  - Rapid response, single IV treatment
- Pamidronate (Aredia®)
  - 1.3-2.0 mg/kg diluted in 250 ml NaCl
  - Give over 2 hours
- Zoledronic acid
  - 0.25 mg/kg dilute in 50-100 ml D5W
  - Give over 15 minutes

**Cholecalciferol - Treatment**
- Wean off saline diuresis
- Send home on oral furosemide, pred, and phosphate binder
  - 2-4 w
- Monitor Ca daily for 5-7 d post diuresis, then 2x w for 2 w, and then weekly
Treatment - When are you done?

- Normal renal values
- Ca X Phos < 60 without ongoing treatment
  - Signs may last for 2-4 weeks as calcifediol has a half life of 16-30 days

Prognosis

- Good if caught early
- Decreases with prolonged elevations of Ca and P
  - Depends upon the degree of soft tissue calcification (renal, cardiac, GI)
  - Lesions from soft tissue mineralization are poorly reversible and may result in long term sequelae or sudden death
  - Rupture of great vessel several months later, at site of calcification

Other Vit D sources

- Vitamins
  - 50,000 IU capsules (1.25 mg)
- Calcipotriene (Dovonex®) Ointment
  - Used to treat psoriasis
- Calcitriol

- Same clinical syndrome and treatment as cholecalciferol rodenticides