Rodenticides: It’s more than just Vitamin K!

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Did you know?

- Incidence rate of rodenticide toxicities in small animals
- In 2013 VPI Pet Insurance received

<table>
<thead>
<tr>
<th>Number of Claims</th>
<th>Total Submitted Fees</th>
<th>Average Cost Per Pet</th>
</tr>
</thead>
<tbody>
<tr>
<td>659</td>
<td>= $210,553</td>
<td>= $425</td>
</tr>
</tbody>
</table>
VPI® and Pet Poison Helpline® working together

- Shared mission in highlighting the importance of preparing for accidents and poisonings in small animals

- Addressing the cost of veterinary care
  - VPI covers the $39 Pet Poison Helpline fee when a pet is brought in to your hospital for care

- Enabling best medicine
  - Pet owners with VPI pet insurance spend 60% more on veterinary care than those without pet insurance
VPI® and Pet Poison Helpline® working together

- Providing veterinary reviewed pet health information online
  - www.petpoisonhelpline.com/owners
  - www.petinsurance.com/healthzone.aspx

- Providing complimentary pet owner educational materials for your practice – available for ordering
  - First Aid for Your Pet brochure
  - Poisoning Emergencies brochure
  - Toxins in the Kitchen stickers
  - Toxic Human Meds stickers
  - Emergency Numbers stickers
Introduction

Ahna G. Brutlag, DVM, MS, DABT, DABVT

Associate Director

Pet Poison Helpline
Minneapolis, Minnesota
Lecture objectives

• Update on new regulations
• 1st vs 2nd generation anticoagulants
• Review of rodenticides: MOA, diagnosis, treatment
  – Long-acting anticoagulant (LAAC)
  – Bromethalin
  – Zinc phosphide
  – Cholecalciferol
EPA regulations have changed!
Residential Products

• New regulations for residential use
  – Blocks bait only (no pellets)
  – No 2nd generation anticoagulants
  – Bait stations mandatory
  – Max size = 1 lb

• Allowed active ingredients
  – 1st gen anticoagulants and non-anticoagulants
    • No bromodialone, brodifacoum, difenacoum, difethialone
    • Bromethalin (neurotoxicant)
    • Cholecalciferol (Vitamin D3)

• Emerging market favorite: Bromethalin (neurotoxicant)
  – No antidote
  – No ante mortem test
  – More difficult treatment
1st gen vs 2nd gen anticoagulants

- **1st generation**
  - Moldy sweet clover poisoning in cattle (1921) → coagulopathy → dicoumarol
  - Synthesis of dicoumarol and WARFARIN (4-hydroxy-coumarin derivative) at UW-Madison (warfarin is longer-acting and more potent)
  - WARFARIN introduced as a rodenticide in 1948

- **2nd generation or “SUPER-WARFARINS”**
  - Increasing warfarin resistance in rodents led to development of newer anticoagulant rodenticides (1960’s-80’s).
  - Examples: bromadiolone, brodifacoum (d-CON)
Why are 2nd gens more toxic than 1st gens?

✓ Greater affinity for vitamin K epoxide reductase enzyme
✓ Additional affinity for cytosolic vitamin K reductase (aka DT-diaphorase)
✓ Accumulation and persistence in the liver
✓ Longer half-life
  – Greater lipid solubility ➔ less ionized, more reabsorption
  – Enterohepatic recycling
Ag/Professional Products

• Only sold in ag store, tractor/farm equipment store
• For use in or around (w/in 50 ft) agricultural buildings

• VERY FEW CHANGES
  – 2\textsuperscript{nd} gen. anticoagulants are allowed (>8 lbs)
  – Non-LAAC are allowed (>4lbs)
  – Pellets, meal, blocks, paste are allowed
Bait Stations

- All consumer baits must be sold with a bait station
  - 4 levels of resistance
    - Weather
    - Child
    - Child and dog
    - Not tested (use in dog/kid inaccessible areas only)

- Problem? Just one station per pound!

http://www.victorpest.com/store/mouse-control/M920
http://findnsave.sfgate.com/Product/24387278/16-oz-Mouse-Killer-Refillable-Bait-Station
1 pound consumer package, bromethalin
Breaking news!

• d-CON (brodifacoum) fought EPA’s decision since 2011
• 5/30/14 settled with EPA
• Switching to diphenacinone in 2015
  – 1st gen anticoagulant
What does this all mean?

• Improved safety?

• More exposure to non-anticoagulant rodenticides?
  – More bromethalin?
    • 65% case increase since 2011 at PPH
  – More rodenticides without antidotes?

• No changes?
PPH 2nd gen anticoagulant vs bromethalin cases (Jul, 2009- May, 2014)
Long-acting Anticoagulants (LAACs)

- Green ≠ long-acting anticoagulants (LAACs)
- Always identify the active ingredient
Anticoagulant rodenticides

• Most common rodenticides
• Inhibit production of Vitamin K dependent clotting factors in the liver
How Do Anticoagulant Rodenticides Work?

Factors II, VII, IX, X (inactive)

Carboxylated Factors II, VII, IX, X (active)

Ca++ added

γ-Carboxylation

Reduced Vitamin K₁ HYDROQUINONE (active)

Oxidized Vitamin K₁ EPOXIDE (inactive)

Cytosolic Vitamin K reductase

Vitamin K epoxide reductase

PET POISON HELPLINE

BLOOD CLOTTING

ANTICOAGULANTS

Vitamin K₁ QUINONE
## Toxic Doses

<table>
<thead>
<tr>
<th>Species</th>
<th>Brodifacoum LD50 (mg/kg, p.o.)</th>
<th>Bromadiolone LD50 (mg/kg, p.o.)</th>
<th>Diphacinone LD50 (mg/kg, p.o.)</th>
<th>Difethiolone LD50 (mg/kg, p.o.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>0.4</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>0.3</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>0.25-4</td>
<td>11-15</td>
<td>0.9-9</td>
<td>4</td>
</tr>
<tr>
<td>Cat</td>
<td>25.0</td>
<td>&gt; 25.0</td>
<td>15</td>
<td>&gt; 16</td>
</tr>
</tbody>
</table>

*In general, treat at 1/5 - 1/10 of the LD50*
Brodifacoum
(finished bait, 0.005%)

Bromadiolone
(finished bait, 0.005%)

Toxic dose for 50 lb dog.
What about cats?

- Remarkably resistant!

- Brodifacoum
  - Canine LD$_{50}$: 0.2-4 mg/kg
  - Feline LD$_{50}$: 25 mg/kg

- Bromadiolone
  - Canine LD$_{50}$: 11-15 mg/kg
  - Feline LD$_{50}$: >25 mg/kg

- Diphacinone
  - Canine LD$_{50}$: 0.9-9 mg/kg
  - Feline LD$_{50}$: 15 mg/kg
Toxic dose comparison

diphacinone, 0.005%

1.6 oz bait

5.3 oz bait!
Course of Poisoning

• Signs begin 3-5 days after ingestion

• Why the delay? Due to plasma $t_{1/2}$ of clotting factors
  – Factor VII and IX = 6 and 14 hr respectively in dogs

• Bleeding is **not** the most common sign!
LAAC: Clinical Signs

- Dyspnea (57%)
- Lethargy (48%)
- Coughing/hemoptysis (30%)
- Pallor (26%)
- Epistaxis (17%)
- Vomiting (17%)
- Melena (17%)
- Hematochezia (13%)
- Lameness (13%)
- Hematoma (15.9%)

- Ecchymoses (13%)
- Hematuria (2.9%)
- Gingival bleeding (9%)
- Collapse (2.9%)
- Anorexia (1.4%)
- Abdominal distension (1.4%)
- Abdominal pain (1.4%)
- Shaking (1.4%)
- **Cats:** Otic hemorrhage
Where’s the blood?

• Intracavital, not serosal bleeds
  
  – *Factor deficiencies ➔ cavital bleeding*  
    (hemothorax, hemoabdomen, coughing blood, bleeding into lungs, pericardial effusion)

  – *Thrombocytopenia or platelet clumping ➔ mucosal and subdermal bleeding*  
    (melena, petechiae, ecchymoses)
Radiographs of clinical LAAC

http://www.boulesdefourrure.fr/
LAAC post mortem
LAAC: Diagnosis

• Presumptive
  – Suspected exposure, appropriate clinical signs
  – Evidence of coagulopathy
    • Prolonged PT/PTT at ≥ 48 hours
    • ACT not specific for LAACS!

• Definitive (less common)
  – Anticoagulant screen
    • Liver, blood, or bait
    • 5-7 day turn around
  – Testing for the presence of:
    • Brodifacoum, bromadiolone, chlorophacinone, coumachlor, difethialone, diphacinone, warfarin

Pachtinger GE, Otto CM, Syring RE. Incidence of prolonged prothrombin time in dogs following gastrointestinal decontamination for acute anticoagulant rodenticide ingestion.
Other Common Lab Results in LAAC Intoxicated Patients

• Packed cell volume (PCV): < 30% (if bleeding)

• PT: 2-6 X normal (preferred test)
  – Most specific for factor VII

• aPPT: 2 - 4 X normal

• Activated coagulation time (ACT): 2 - 10 X normal

• Platelets: normal to mild thrombocytopenia

• Fibrin degradation products (FDPs): normal (test of fibrinolytic system)
LAAC antidote: Vitamin K₁

- **Oral** – preferred route
  - Absorbed faster than parenteral due to small intestinal lymphatics
  - Enhanced w/ fatty meal
  - 2.5-5mg/kg SID or divided BID

- **Parenteral**
  - Give SQ only
  - Rarer: IM - hematoma risk
  - Never: IV - anaphylactoid reactions
Treating an acute ingestion

- **Option #1**—Determine with PT test
  - Emesis + activated charcoal
  - Check PT in 36 hrs
  - Vitamin K₁ if needed

  OR

- **Option #2**—Prophylactic Vitamin K
  - Decontamination + activated charcoal + Vitamin K₁ X 30 days
    - No need to check PT while on Vit K₁
    - Give orally only
  - Recheck PT 48 hours after last dose of Vit K₁ therapy!
    - If prolonged, repeat X 2 weeks; repeat PT 48 hrs after last dose.
Bromethalin
Bromethalin

• Bromethalin vs. brodifacoum vs. bromadiolone?

• METHAMPHETAMINE addict

• Central nervous system (CNS) signs!
Bromethalin

- Blocks, pellets, or worms

- **Cats more sensitive than dogs**

- **Dog LD$_{50}$**: 3.7 mg/kg
  - Lowest toxic dose reported 1-1.5mg/kg

- **Cat LD$_{50}$**: 0.54 mg/kg
  - Lowest toxic dose reported 0.24mg/kg
Bromethalin: CNS Toxicity

Cerebral and spinal cord edema $\Rightarrow$ ↑intracranial pressure $\Rightarrow$ neurological disturbances $\Rightarrow$ paralysis or convulsions $\Rightarrow$ DEATH

Diffuse spongiosis of cerebral cortical white matter from a dog given bromethalin (6.25 mg/kg) 40 hours earlier.
Toxic Syndromes in Cats and Dogs

- **Paralysis** (any toxic dose)
- **Paralysis** (toxic dose < LD50)
- **Convulsions** (toxic dose > LD50)
Clinical Signs

• Paralytic syndrome
  – Dogs: ingestions of > 1 mg/kg but < 3.7 mg/kg
  – Cats: > 0.24 mg/kg
  – Onset: 1-4 days
  – Progression: days to weeks
  – Hind limb ataxia, weakness, ↓CP’s → paralysis
  – Cats: abdominal distension, ileus, increased urethral tone

• Convulsant syndrome
  – > LD_{50} ingestions
  – 2-24 hours to onset, progression rapid
  – Tremors, hyperthermia, hyperexcitement, seizures
Rear limb ataxia with decreased conscious proprioception in a cat 5 days after experimental dosing of 0.45 mg/kg of bromethalin.

Courtesy of Dr. David Dorman, NCSU.
Experimental bromethalin intoxication in a cat. Animals placed on their back exhibit extensor rigidity (left image) and a lack of conscious proprioception (unable to place their feet appropriately) (right image) of all four limbs.

Courtesy of Dr. David Dorman, NCSU.
Diagnosis

• History of ingestion with clinical signs
• Routine lab tests are not helpful
• **Differentials:** Signs of toxicity mimic those of many other CNS diseases (lead toxicity, tumors, ethylene glycol, head trauma, rabies, distemper)
• Post mortem (definitive diagnosis)
  – Bromethalin may be detected by gas chromatography in stomach contents, kidney, and brain
  – Histopathological exam of CNS structures shows diffuse vacuolation in white matter (spongiform degeneration) with microgliosis
A swollen axon (A) with intramyelinic vacuolization (B) in the brainstem of a dog fed 6.25 mg/kg bromethalin 40 hours prior.

Courtesy of Dr. David Dorman, NCSU.
Treatment

• Early and aggressive decontamination
  – Emesis or gastric lavage
  – Activated charcoal, repeated doses due to enterohepatic recirculation – check Na with sudden onset signs

• Monitor for signs of cerebral edema!
Bromethalin: Treatment

• Treatment for cerebral edema
  – r/o hypernatremia from charcoal first!

• Reducing intracranial pressure (ICP)
  – 15-30° head elevation
  – Mannitol (0.5 - 1.5 g/kg infusions or CRI)
  – Furosemide? (1-2 mg/kg, IV in conjunction with mannitol)

• Perfusion, perfusion, perfusion!
  – Oxygen supplementation
  – IV fluids to maintain cerebral perfusion pressure (CPP)
  – Steroids? NO!
Bromethalin: Treatment

- **Anticonvulsants**
  - Phenobarbital 4-16 mg/kg IV PRN
  - Diazepam 0.25-1 mg/kg IV PRN

- **Antiemetics (prevent aspiration!)**
  - Maropitant 1 mg/kg SQ q. 24

- **Thermoregulation**
  - Keep cool vs hot
Zinc Phosphide
Toxic Dose

• Mole & gopher bait

• Canine LD$_{50}$ = 20-50 mg/kg
  – Reports of surviving 300 mg/kg

• Toxicity increases in presence of gastric acid.
Mechanism of Action

• Undergoes hydrolysis → phosphine gas
  – Acidic or moist environment

• Poison: Phosphine gas (not zinc)
  – Direct corrosive effects on the gastrointestinal tract (esophagus, stomach and duodenum)
  – Rapidly absorbed from the mucosa and systemically distributed
Clinical Signs

• GI
  Vomiting, diarrhea, anorexia, abdominal pain

• CNS
  Malaise, altered mentation, behavior changes, ataxic, tremors, seizures

Clinical Signs

• Cardiovascular
  • Tachycardia, shock

• Respiratory
  • Tachypnea, pulmonary edema

Treatment

• **DO NOT FEED!**

• Decontamination
  • Emesis
    – In a well ventilated area
    – Consider liquid antacid prior or lavage with 5% NaHCO₃
  • Activated charcoal?

• **IV fluids**

• Symptomatic and supportive care
  • Anti-emetic therapy
Public Health Risk

• Exposure associated with patient emesis

• Inhalation of phosphine gas reported to cause
  – Nausea
  – Headaches

Cholecalciferol

“It said ‘Vitamin’ on it, Doc!”
Cholecalciferol (Vit D3)

• Promotes calcium retention
  – ↑ Ca and phos absorption from the GIT
  – ↑ Ca reabsorption from the distal tubules
  – ↑ Ca mobilization from the bones

• Toxicosis results in
  – Hypercalcemia (total serum calcium and iCa)
  – Hyperphosphatemia
  – Metastatic tissue calcification

• Enterohepatic recirculation occurs
Clinical Signs

• Initial signs at 12-48 hrs

• Malaise, weakness, anorexia, PU/PD, vomiting, melena, hematemeses, and dehydration

• Progression to acute renal failure (and chronic)
Diagnosis

- **Within 12-24 hours:**
  - $\uparrow P > 8.0 \text{ mg/dL (w/in 12-24hrs)}$
  - $\uparrow P$ often earlier than Ca

- **Within 24-36 hours:**
  - $\uparrow \text{Ca} > 12.5 \text{ mg/dL}$

- **Within 24-48 hours:**
  - +/- $\uparrow \text{BUN/creatinine}$

- **Monitor labs q 12 - 24hrs**

- **Vitamin D panel**
  - PTH, ionized calcium, and 25-hydroxyvitamin D
Cholecalciferol

Must treat aggressively!

CRF!
Treatment

• Decontamination:
  – Emesis induction
  – Activated charcoal q 4-6 hours X 4 doses
  – Undergoes enterohepatic recirculation

• IV Fluids
  – 0.9% NaCl diuresis for days!
  – Promotes calciuresis
Treatment

• Gastrointestinal support:
  – Phosphate binders
  – Antiemetics
  – H₂ blockers
  – Sucralfate

• Monitoring:
  – Venous blood gas/ionized calcium or total serum Ca
  – Renal panel q 24 hours while hospitalized, then 2-3 days thereafter
  – Frequent rechecks
Treatment

- **Diuretics:** furosemide 2-4 mg/kg q 8-12hrs
  - ↑ calciuresis

- **Steroids:** prednisone 2 mg/kg q 12hrs
  - ↑ calciuresis, ↓ GI absorption, ↓ bone resorption

- **Bisphosphonates**
  - ↓ bone resorption; direct and indirect affect on osteoclasts
    - Pamidronate 1.3-2mg/kg IV may need to repeat
    - Clodronate 4mg/kg IV dosing, orally?

**CORRECT DEHYDRATION BEFORE INITIATING DIURETICS OR STEROIDS!**
When in doubt, call for assistance!

- Know the active ingredient!
- Don’t just reach for Vitamin K!
- Call for something you’re not familiar or comfortable with.
- Don’t forget the odd ones:
  - Cholecalciferol
  - Bromethalin
  - Zinc phosphide
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