

# WITH BAITED BREATH... ADDRESSING RODENTICIDE INTOXICATION



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## SO MANY OPTIONS...

Diphacinone



Brodifacoum



Corn gluten  
+ NaCl



**ALWAYS ASK  
OWNER FOR  
PACKAGING IF  
AVAILABLE**



Zinc  
phosphide



Cholecalciferol



## BRIEF HISTORY OF RODENTICIDES

- 1940s-1950s: Warfarin and other first-generation anticoagulants developed as rodenticides
- 1970s-1980s: Emergence of resistance to first generation products among rodent populations
  - Development of second-generation anticoagulants
  - Introduction of non-anticoagulant rodenticides
- 2008-2014: EPA drafts and implements "Risk Mitigation Decision for Ten Rodenticides", aimed at:
  - Minimizing risk to children in homes
  - Reducing wildlife exposures and ecological risks



## ANTICOAGULANT RODENTICIDES

- First generation
  - Warfarin, pindone, chlorphacinone, diphacinone
  - Higher median lethal doses
  - Often require multiple ingestions to cause mortality
- Second generation
  - Brodifacoum, bromadiolone, difethiolone, difenacoum
  - Lower median lethal doses
  - Typically cause mortality with a single ingestion

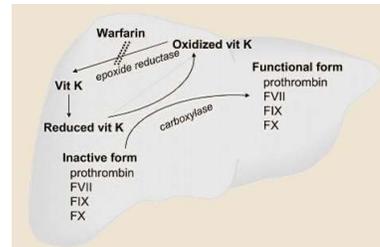


## CLASSES OF RODENTICIDE

- **Anticoagulants**
  - Diphacinone
  - Chlorphacinone
  - Brodifacoum
  - Difenacoum
  - Bromadiolone
  - Warfarin
- **Bromethalin**
- **Cholecalciferol**
- Zinc phosphide (mole and gopher bait)
- Corn gluten + NaCl



## ANTICOAGULANT RODENTICIDES: MECHANISM OF ACTION



\*Stroke Manual: stroke-manual.com/warfarin/



## ANTICOAGULANT RODENTICIDES: CLINICAL PRESENTATION

- May present **asymptomatic** if ingestion occurred within 24-48 hours
  - Packaging or pellets/blocks found in environment
  - Rodenticide visualized in stool

Half-life of affected coagulation factors (II, VII, IX, X) ranges from 6.2-16.5 hours

Circulating factors exhausted over 24-64 hours

Prolongation of coagulation parameters (PT/PTT) and clinical bleeding are therefore delayed 2-5 days following ingestion

## ANTICOAGULANT RODENTICIDES: DECONTAMINATION

- Only indicated in **non-clinically** affected patients



- Induction of emesis within 4 hours of ingestion
  - Dogs: Apomorphine 0.02-0.05 mg/kg IV
  - Cats: Dexmedetomidine 7-10 mcg/kg IM, 10-20 mcg/kg OTM
- Activated charcoal with cathartic (sorbitol) 1g/kg PO - Optional
- Consider enema if rodenticide visible on rectal exam

## ANTICOAGULANT RODENTICIDES: CLINICAL PRESENTATION

- Clinical signs reflect **bleeding** and resulting **anemia**
  - Lethargy
  - Weakness or collapse
  - Pallor
  - Tachypnea
  - Tachycardia
  - Hypotension
- **Location** of bleeding affects specific signs
  - Respiratory distress
  - Abdominal distention
  - Hematemesis, melena, hematochezia
  - Hematoma formation
  - Ataxia, seizures
  - Joint pain
- Petechiation and ecchymoses are not typically a result of coagulopathy – consider platelet disorder



## ANTICOAGULANT RODENTICIDES: TREATMENT

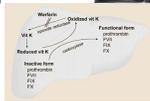
- Oxygen supplementation, if needed
- Fluid resuscitation, if indicated
- Fresh frozen plasma or fresh whole blood given until coagulation parameters normalize
  - Supplies active clotting factors
- Packed red blood cells
  - Addresses severe anemia following normalization of coagulation parameters
  - Ideally, correct coagulopathy first
- Supportive care, as indicated
- Vitamin K1 to facilitate regeneration of active clotting factors
  - 3-8mg/kg/day, divided BID for **28 days**
  - Avoid IM and IV administration
  - Oral administration preferred – give with fatty meal to enhance absorption
  - SC administration with small gauge needle (25g) may be given initially
- Activity restriction



## ANTICOAGULANT RODENTICIDES: DIAGNOSIS

- History / Exposure
- Compatible clinical signs
- CBC or PCV/TS
- Prothrombin time (PT) and Partial thromboplastin time (PTT)
  - PT elevation occurs earlier due to shorter half-life of factor VII
- Imaging

- PIVKA (protein induced by Vitamin K absence/antagonism)
  - Lacks specificity for rodenticide-induced coagulopathy
- Anticoagulant screening (gastric contents, serum, plasma, liver, kidney)
  - Typically not pursued



## ANTICOAGULANT RODENTICIDES: MONITORING

- If ingestion is uncertain:
  - No treatment – Check PT/PTT in 48-72 hours
  - Prophylactic treatment with Vitamin K1 – Check PT/PTT 48-72 hours after last dose
- If asymptomatic:
  - Check PT/PTT 48-72 hours after last dose of Vitamin K1
- If coagulopathic:
  - Recheck PT/PTT following FFP or whole blood transfusion until normalized
  - Monitor PCV/TS
  - Check PT/PTT 48-72 hours after last dose of Vitamin K1

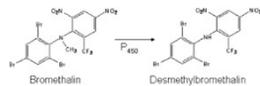
## ANTICOAGULANT RODENTICIDES: PROGNOSIS

- Early intervention
- Aggressive appropriate treatment
- Client compliance
- Location of bleeding

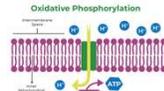
## BROMETHALIN: CLINICAL PRESENTATION — PARALYTIC SYNDROME (DOGS)

- Lower dose ingestion in dogs (< LD50)
- Onset of signs 1-4 days post-ingestion, with progression over 1-2 weeks
- Early signs:
  - Hind limb weakness
  - Ataxia
- Later signs:
  - Depression
  - Tremors
  - Hyper-reflexive hind limb paralysis
  - Decreased conscious proprioception
  - Loss of deep pain
- Other possible signs:
  - Vomiting, anorexia
  - Anisocoria, opisthotonos, seizures, coma, death

## BROMETHALIN: MECHANISM OF ACTION

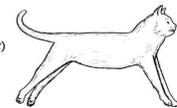


- Bromethalin metabolized to desmethylbromethalin via N-demethylation in the liver
    - Desmethylbromethalin is major toxic metabolite
  - Uncouples oxidative phosphorylation in mitochondria
    - Decreased cellular ATP production
      - Failure of Na<sup>+</sup>, K<sup>+</sup>-ATPase pumps
        - Cells lose osmotic control – retain sodium intracellularly
          - Intramyelinal edema
- Edema of the brain and spinal cord lead to decreased nerve impulse conduction leading to two possible clinical syndromes



## BROMETHALIN: CLINICAL PRESENTATION — PARALYTIC SYNDROME (CATS)

- Most cats, regardless of dose
- 3x more sensitive than dogs
  - LD<sub>50</sub>: 0.54mg/kg
  - Signs at doses as low as 0.24mg/kg
- Onset of signs 1-4 days post-ingestion, with progression over 1-2 weeks
- Signs similar to canine paralytic syndrome
- Additional signs:
  - Abdominal distention (ileus)
  - Inability to urinate (increased urethral tone, UMN bladder)
- End-stage:
  - Decerebrate posture

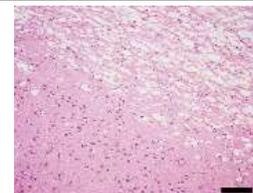


## BROMETHALIN: CLINICAL PRESENTATION — CONVULSANT SYNDROME

- Higher dose ingestion in dogs (> LD<sub>50</sub>: 2.38-5.6mg/kg)
- Onset of signs 4-36 hours post-ingestion
- Hyperexcitability
- Hyperthermia
- Tremors
- Focal and generalized motor seizures (may be sound- or light-induced)

## BROMETHALIN: DIAGNOSIS

- History of exposure
- Compatible clinical signs
- BG, electrolytes, PCV/TS
- No pathognomonic abnormalities
- Liquid chromatography/mass spectrometry – detection of desmethylbromethalin
  - Adipose, kidney, brain, liver, bait
- Characteristic CNS lesions post-mortem
  - Mild to moderate cerebral edema
  - White matter spongiosis from widespread myelin vacuolization
  - Absence of inflammation



Pathology in Practice: <https://doi.org/10.2460/javma.21.08.2020>

## BROMETHALIN: DECONTAMINATION

- Early and aggressive
- Induction of emesis, if asymptomatic
- Gastric lavage
- Enema
- Multiple doses of activated charcoal
  - Both bromethalin and desmethylbromethalin undergo enterohepatic recirculation
- Protocol may delay onset and reduce magnitude of signs in dogs
  - Multiple doses of activated charcoal may be less beneficial in cats
- 1 oz 0.01% bromethalin bait contains 2.84mg bromethalin

TABLE 1 The ASPCA APCC's Decontamination Recommendations for Bromethalin Ingestion		
Time Since Exposure	Dose Ingested <sup>a</sup>	Action
<b>Dogs</b>		
< 4 hours	0.1-0.49 mg/kg	Emesis or one dose of activated charcoal
> 4 hours	0.1-0.49 mg/kg	One dose of activated charcoal
< 4 hours	0.5-0.75 mg/kg	Emesis and three doses of activated charcoal over 24 hours
> 4 hours	0.5-0.75 mg/kg	Three doses of activated charcoal over 24 hours
< 4 hours	> 0.75 mg/kg	Emesis and three doses of activated charcoal a day for 48 hours
> 4 hours	> 0.75 mg/kg	Three doses of activated charcoal a day for 48 hours
<b>Cats</b>		
< 4 hours	0.05-0.1 mg/kg	Emesis or one dose of activated charcoal
> 4 hours	0.05-0.1 mg/kg	One dose of activated charcoal
< 4 hours	0.1-0.3 mg/kg	Emesis and three doses of activated charcoal over 24 hours
> 4 hours	0.1-0.3 mg/kg	Three doses of activated charcoal over 24 hours
< 4 hours	> 0.3 mg/kg	Emesis and three doses of activated charcoal a day for 48 hours
> 4 hours	> 0.3 mg/kg	Three doses of activated charcoal a day for 48 hours

<sup>a</sup>Note: 1 oz 0.01% bromethalin bait contains 2.84 mg of bromethalin.

Veterinary Medicine, Duanyer, Eric. Bromethalin: The other rodenticide. Sept. 2003.

## BROMETHALIN: PROGNOSIS

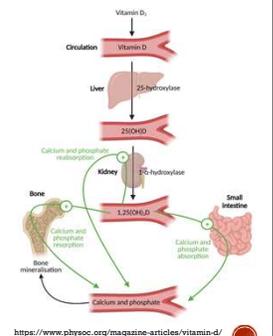
- Half-life of bromethalin ~6 days in rats (undetermined but likely similar in dogs and cats)
  - Clinical signs (hind limb weakness) may persist for weeks or be permanent
- Poor to grave prognosis for survival when convulsant syndrome or complete paralysis develops

## BROMETHALIN: TREATMENT

- No antidote!
- Typically ineffective
  - Edema may be more difficult to mobilize due to accumulation within myelin sheaths
- Clinical signs of intoxication warrant symptomatic and supportive care
  - Seizure/tremor control
    - Mannitol
    - Methocarbamol
    - Anti-seizure drugs
  - Hydration and nutritional support
  - Nursing care for recumbent animals
- Ginkgo biloba
  - Rat study: 100mg/kg dose given at same time as bromethalin
  - Reduced development of cerebral edema and lipid peroxidation
  - Unknown long-term efficacy, usefulness in other species, and efficacy after onset of signs

## CHOLECALCIFEROL: MECHANISM OF ACTION

- Cholecalciferol
  - Calcifediol
  - Calcitriol
- Promotes intestinal absorption of calcium
- Stimulates bone resorption of calcium
- Enhances renal tubular reabsorption of calcium
- **Increased serum calcium**
  - Acute kidney injury
  - Cardiovascular abnormalities
  - Tissue mineralization



## BROMETHALIN: MONITORING

- Clinical monitoring
  - Convulsant signs within 4-36 hours
  - Paralytic signs over 1-2 weeks
- Hydration and serum [Na<sup>+</sup>] prior to activated charcoal administration

## CHOLECALCIFEROL: CLINICAL PRESENTATION

- Clinical signs and laboratory abnormalities often noted within 12-48 hours
- Minimum toxic dose 0.5mg/kg
  - 1oz 0.075% cholecalciferol bait contains 21.28mg cholecalciferol
- Depression
- Lethargy and weakness
- Inappetence
- PU/PD
- Vomiting
- Diarrhea
- Bradycardia and other arrhythmias
- Signs and elevations of Calcium and Phosphorus expected to develop within 72-96 hours

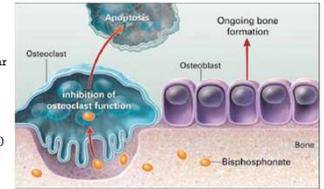
## CHOLECALCIFEROL: DIAGNOSIS

- Minimum recommended baseline:
  - Calcium (ionized is ideal) and Phosphorus
  - BUN and Creatinine
  - Electrolytes
  - PCV/TS
  - USG
- Serial measurement recommendations and treatment based on dose ingested and clinical signs
- Post-mortem findings:
  - Mineralization and necrosis of GI, cardiac, and renal tissues



## CHOLECALCIFEROL: TREATMENT & MONITORING - SYMPTOMATIC

- 0.9% NaCl IV fluid therapy (2x maintenance)
  - NaCl causes calciuresis
    - Na<sup>+</sup> and Ca<sup>++</sup> ions compete for reabsorption
    - Na-Ca exchanger on basolateral membrane of tubular cells of the distal convoluted tubule
- Pamidronate
  - Decreases osteoclastic bone activity
  - 1.3-2.0mg/kg IV infusion over 2 hours (1.3mg/kg in cats)
  - Significant improvement/normalization within 1-3 days



N Engl J Med. 2002; 346:642.



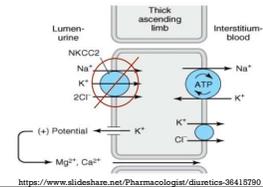
## CHOLECALCIFEROL: DECONTAMINATION

- Induction of emesis within 4 hours of ingestion
- Activated charcoal, dose-dependent
  - 0.1-0.5mg/kg Cholecalciferol:
    - Single dose Activated charcoal 1g/kg with cathartic
  - >0.5mg/kg Cholecalciferol:
    - Initial dose Activated charcoal 1g/kg with cathartic
    - 2-3 additional doses Activated charcoal 0.5-1g/kg without cathartic q6-8h



## CHOLECALCIFEROL: TREATMENT & MONITORING - SYMPTOMATIC

- Prednisone/Prednisolone
  - Decreases GI absorption, reduces bone resorption, and increases renal excretion
  - 1mg/kg PO q12h, taper as Calcium level improves
- Furosemide
  - Promotes renal excretion of Calcium
  - 2.5-4.5mg/kg q6-8h or 5mg/kg/hr CRI
  - Monitor hydration and electrolytes



https://www.slideshare.net/Pharmacologist/diuretics-36418790



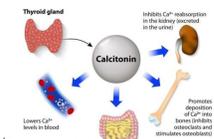
## CHOLECALCIFEROL: TREATMENT & MONITORING - ASYMPTOMATIC

- 0.1-0.5mg/kg Cholecalciferol:
  - Subcutaneous fluid therapy
  - Recheck Calcium, Phosphorus, BUN, Creatinine, PCV/TS, body weight 72 hours post-ingestion (sooner if clinical signs noted)
- >0.5mg/kg Cholecalciferol:
  - IV fluid therapy (2x maintenance) x 24 hours
  - Cholestyramine 0.3-1g/kg PO q8h x 3-4 days
    - Spaced between Activated charcoal during first 24 hours
  - Recheck Calcium, Phosphorus, BUN, Creatinine, PCV/TS, body weight q24h until 96 hours post-ingestion
  - Recheck sodium prior to each dose of activated charcoal



## CHOLECALCIFEROL: TREATMENT & MONITORING - SYMPTOMATIC

- Calcitonin
  - Risk of anaphylaxis
  - Often refractory with multiple doses
  - Avoid administration in combination with Pamidronate
    - Increases risk of soft tissue mineralization
- Aluminum hydroxide
  - Dietary phosphate binding in hyperphosphatemic patients
  - 30-90mg/kg/day PO, divided with each meal
- GI support as needed
  - Recheck Calcium, Phosphorus, BUN, Creatinine, PCV/TS, body weight q12-24h until 96 hours post-ingestion
  - Recheck sodium prior to each dose of activated charcoal



https://www.vectorstock.com/royalty-free-vector/calcitonin-thyroid-hormone-vector-40745098



## CHOLECALCIFEROL: PROGNOSIS

- Dependent on dose ingested and clinical course/intervention
- Long half-life of cholecalciferol (>17 days)
  - Prolonged clinical signs
  - Weeks of laboratory monitoring
  - Ongoing adjustments to treatment
- Metastatic calcification can result in chronic systemic disease, such as CKD
  - May require long-term management



## ZINC PHOSPHIDE: DIAGNOSIS

- History of ingestion/exposure
- Acetylene or fishy odor to breath
- CBC
- Chemistry
  - Elevated liver enzymes, esp. ALP
  - Azotemia
  - Hypoglycemia
- Venous blood gas
  - Metabolic acidosis
- Liquid gas chromatography of vomitus or frozen stomach contents (airtight samples)



## ZINC PHOSPHIDE: MECHANISM OF ACTION

- Liberation of phosphine gas:  $Zn_3P_2 + 6 H_2O = 3 Zn(OH)_2 + 2 PH_3$ 
  - Favored under moist and acidic conditions
  - Phosphine gas absorbed from GI tract and respiratory mucosa
- Results in an increase in reactive oxygen species (ROS) causing oxidative injury to multiple organ systems
  - Brain, liver, lungs, heart, kidneys
- Disrupts aerobic respiration and cellular energy production at mitochondrial level
- May inactivate acetylcholinesterase
- Acts as a direct gastric irritant



## ZINC PHOSPHIDE: DECONTAMINATION (& BEFORE)

- Prior to arrival at veterinary facility:
  - Avoid feeding (food stimulates gastric acid secretion, lowering pH)
  - Antacids to increase gastric pH
    - Magnesium hydroxide
    - Calcium carbonate
- Asymptomatic animals:
- Induction of emesis within 1-2 hours of ingestion
  - **Well-ventilated environment**
- Single dose of activated charcoal with sorbitol



## ZINC PHOSPHIDE: CLINICAL PRESENTATION

- Signs may develop within minutes to several hours
  - Lethargy
  - Severe GI distress, may be hemorrhagic
  - Gastric distension
  - Ataxia, tremors, seizures, hyperesthesia
  - Pulmonary edema
  - Tachycardia or bradycardia, pallor, shock
  - Renal and hepatic damage
  - Coagulopathy
  - Methemoglobinemia
  - Death, usually within 3-48 hours of ingestion



## ZINC PHOSPHIDE: TREATMENT

- GI supportive care
  - Aluminum hydroxide, magnesium hydroxide, calcium carbonate
  - Proton pump inhibitors
  - H2 blockers
  - Sucralfate
- IV fluid therapy x 24 hours (or until signs resolve)
  - Control electrolyte abnormalities
  - Address acid-base disturbances
  - Address hypoglycemia
- Methocarbamol IV as needed for tremors
- Anticonvulsants IV as needed for seizures



## ZINC PHOSPHIDE: TREATMENT — ANTIOXIDANT THERAPY

- Antioxidants reduce phosphine-induced ROS formation, lipid peroxidation, and DNA oxidation
- Glutathione – a potent antioxidant (hydroxyl radical scavenger), exists as glutathione disulfide (reduced form)
- **N-acetylcysteine** (IV or PO) and S-adenosylmethionine, or SAM-e, (PO only) provide precursors for glutathione disulfide
  - Stimulates glutathione disulfide synthesis
  - Enhances glutathione-S-transferase activity
  - Promotes detoxification
  - Acts directly on ROS, capable of reducing hydroxyl radicals and hydrogen peroxide
  - Increases intracellular glutathione disulfide concentrations in RBC, hepatocytes, and lung cells



## ZINC PHOSPHIDE: PROGNOSIS

- **Good**
  - Clinically normal 12 hours after ingestion
  - Clinically affected without progression of signs over 24 hours
- **Guarded**
  - Abnormal neurologic status
  - Multiorgan involvement



## ZINC PHOSPHIDE: TREATMENT — ANTIOXIDANT THERAPY

- N-acetylcysteine – available as 10% or 20% solutions
  - Labeled for oral use in US, but used IV
- Dilute to 5% or less
- Use a 0.2micron filter
- 140mg/kg IV loading dose
- 70mg/kg IV q6h x 7-17 doses



## CORN GLUTEN + NaCl

- "ALL NATURAL"
- "NON-TOXIC"
- Causes dehydration and GI obstruction in rats and mice
- Usually only causes GI upset in dogs and cats
- Large volume ingestion can lead to dehydration or obstruction



## ZINC PHOSPHIDE: MONITORING

- Clinical signs
- Serial chemistry and venous blood gas
- Coagulation profile
- ECG
- Thoracic radiographs
- Vitals and BP
- Liver profile 3-5 days after ingestion



## RODENTICIDE SUMMARY

- Identification of active ingredient is vital
- **Early intervention for best prognosis**
  - **Anticoagulants** – result in coagulopathy and spontaneous bleeding
    - Vitamin K1 for 28 days
    - Coagulation factor replacement (FFP, whole blood)
  - **Bromethalin** – results in neurotoxicity (convulsant and paralytic syndromes)
    - No antidote
    - Decontamination – early and aggressive
  - **Cholecalciferol** – results in hypercalcemia
    - Fluid therapy
    - Ca-reducing medications
    - Extended course of treatment and monitoring
    - Risk of long-term effects
  - **Zinc phosphide** – results in phosphine gas and oxidative injury
    - Antacids
    - Antioxidants



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