PET POISON HELPLINE

SAVING PETS' LIVES, 24 HOURS A DAY, 7 DAYS A WEEK

Rodenticides: It's more than just Vitamin K!

June 10, 2014

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Did you know?

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

Number of Claims	Total Submitted Fees	Average Cost Per Pet
659	= $210,553	= $425

VPI® and Pet Poison Helpline® working together

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

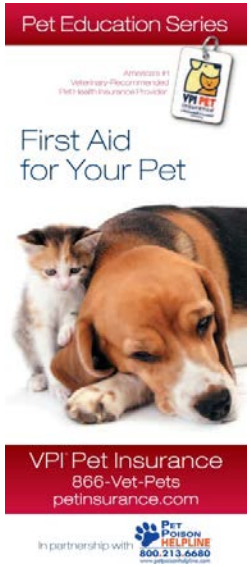
- Addressing the cost of veterinary care
  - VPI covers the $39 Pet Poison Helpline fee when a pet is brought in to your hospital for care

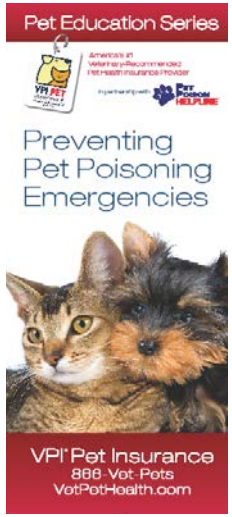
- Enabling best medicine
  - Pet owners with VPI pet insurance spend 60% more on veterinary care than those without pet insurance

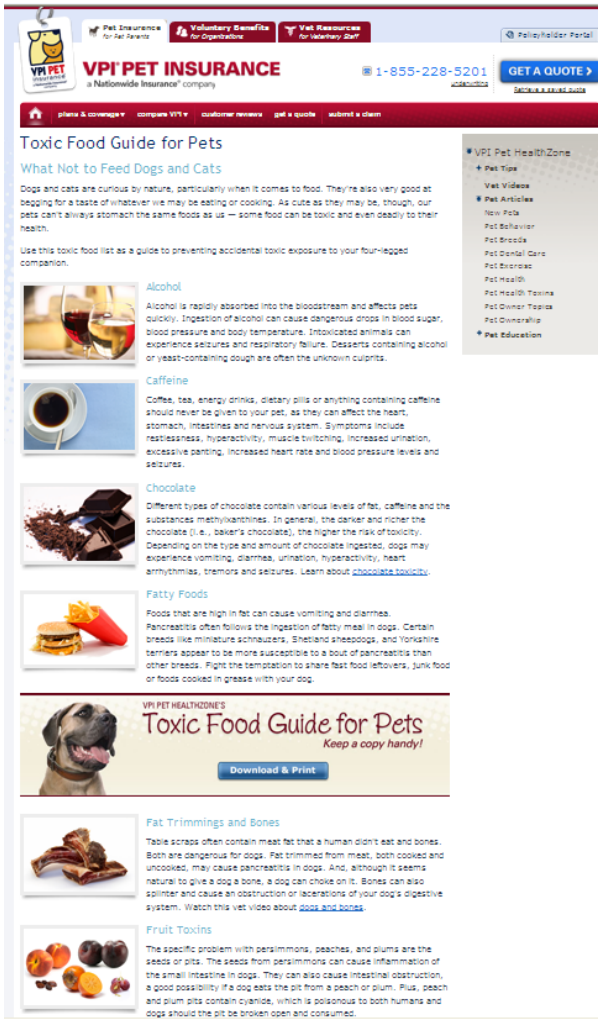
VPI® and Pet Poison Helpline® working together

- 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
  - 2nd 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

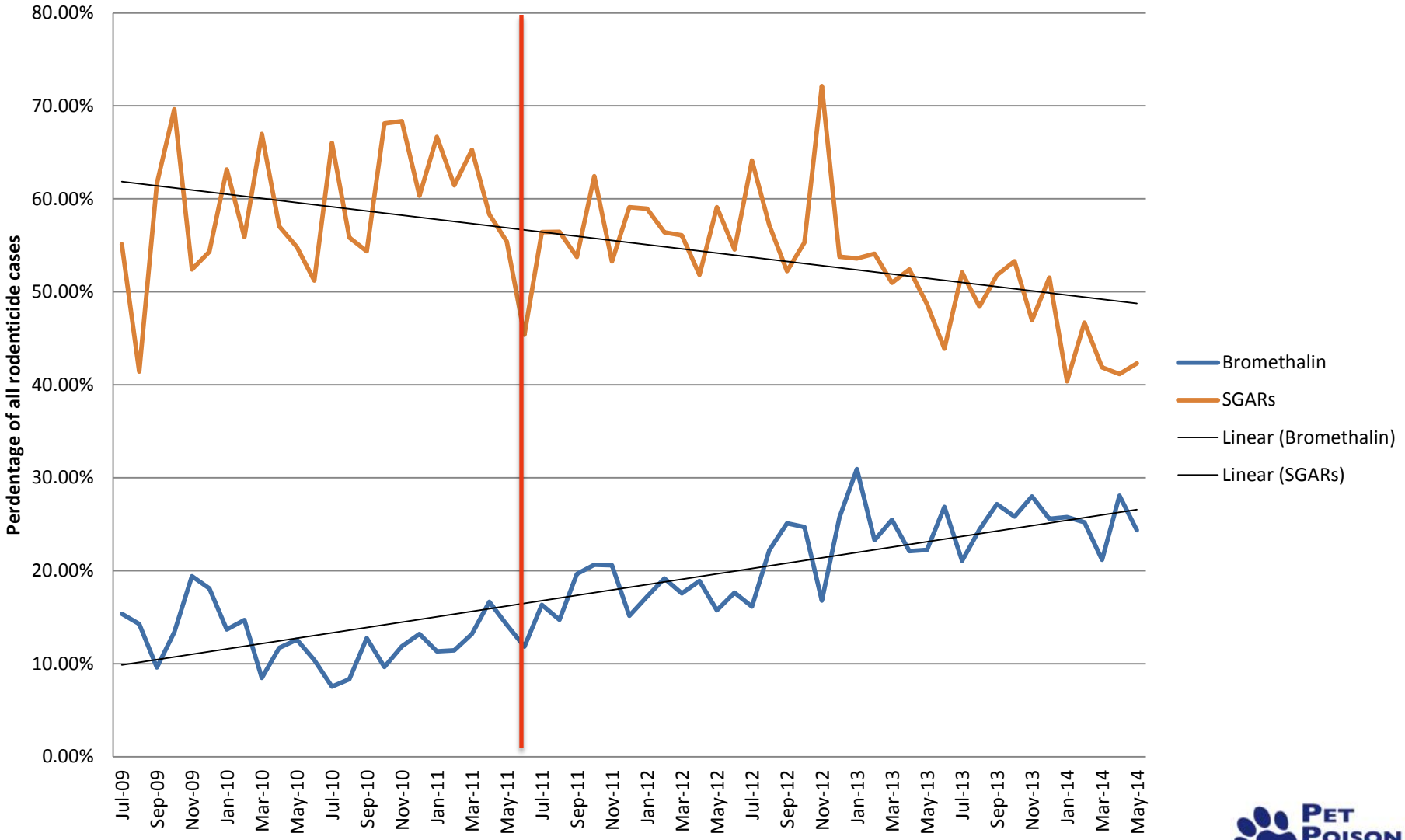
Breaking news!

- d-CON (brodifacoum) fought EPA's decision since 2011
- 5/30/14 settled with EPA
- Switching to diphacinone 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?

BLOOD CLOTTING

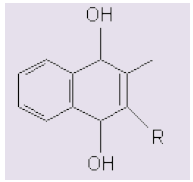
Ca^{++} added

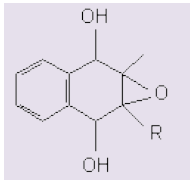
Factors II, VII, IX, X (inactive)

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

γ-Carboxylation

Reduced Vitamin K_1 HYDROQUINONE (active)



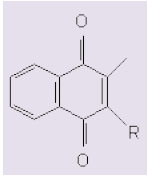


Oxidized Vitamin K_1 EPOXIDE (inactive)

Cytosolic Vitamin K reductase

Vitamin K_1 QUINONE

ANTICOAGULANTS



ANTICOAGULANTS

Vitamin K epoxide reductase

Toxic Doses

Species	Brodifacoum LD50 (mg/kg, p.o.)	Bromadiolone LD50 (mg/kg, p.o.)	Diphacinone LD50 (mg/kg, p.o.)	Difethiolone LD50 (mg/kg, p.o.)
Mouse	0.4	1.0		
Rat	0.3	0.7		
Dog	0.25-4	11-15	0.9-9	4
Cat	25.0	> 25.0	15	>16

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!

- Brodifaoum
  - 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

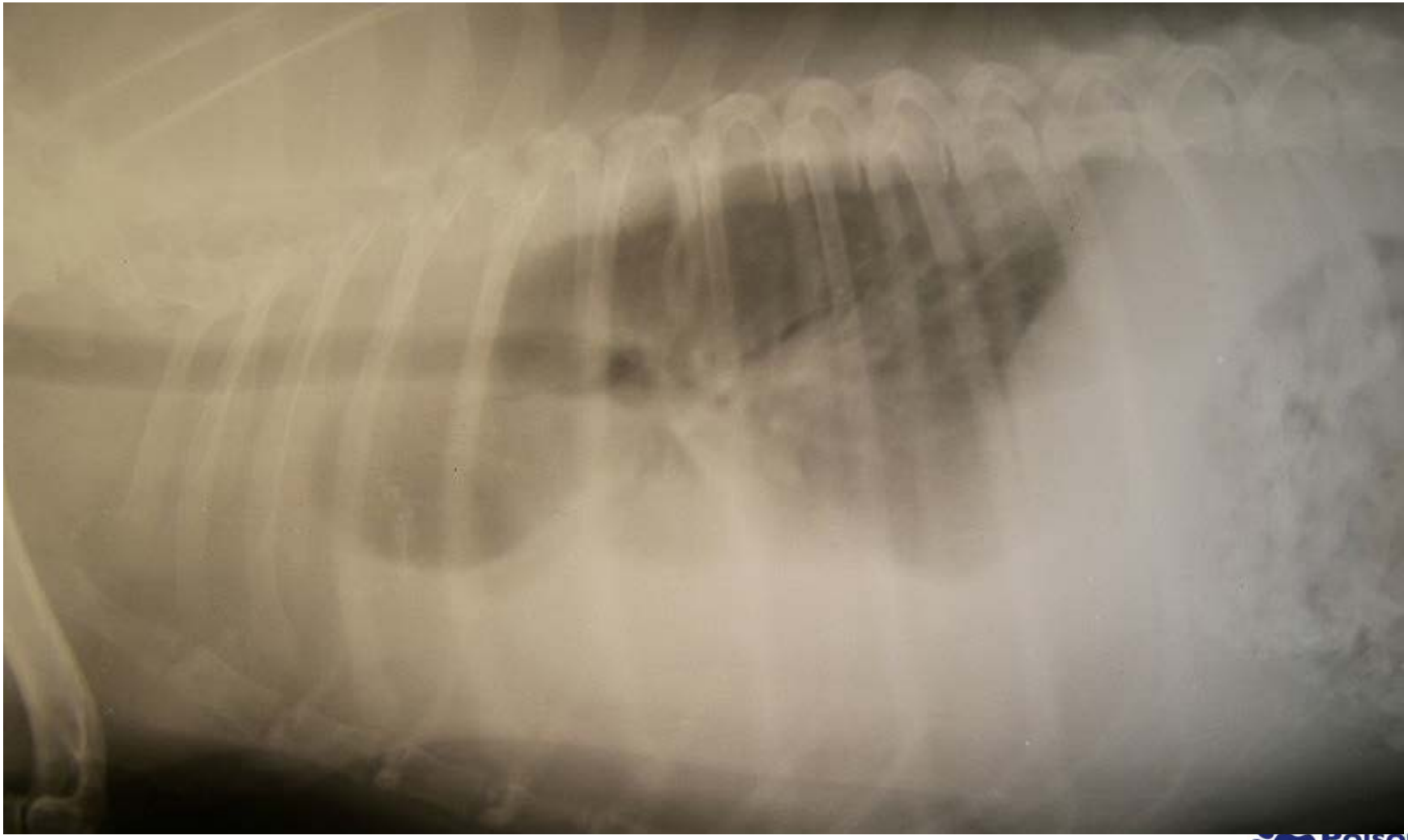
Sheafor SE, Couto CG. Anticoagulant Rodenticide toxicity in 21 dogs. J Am Anim Hosp Assoc. 1999;30:38-46

Bohn B, Weingart, Giger U. Hemorrhage in seven cats with suspected anticoagulant rodenticide intoxication. J Fel Med Surg 2003;5:295-304

Where's the blood?

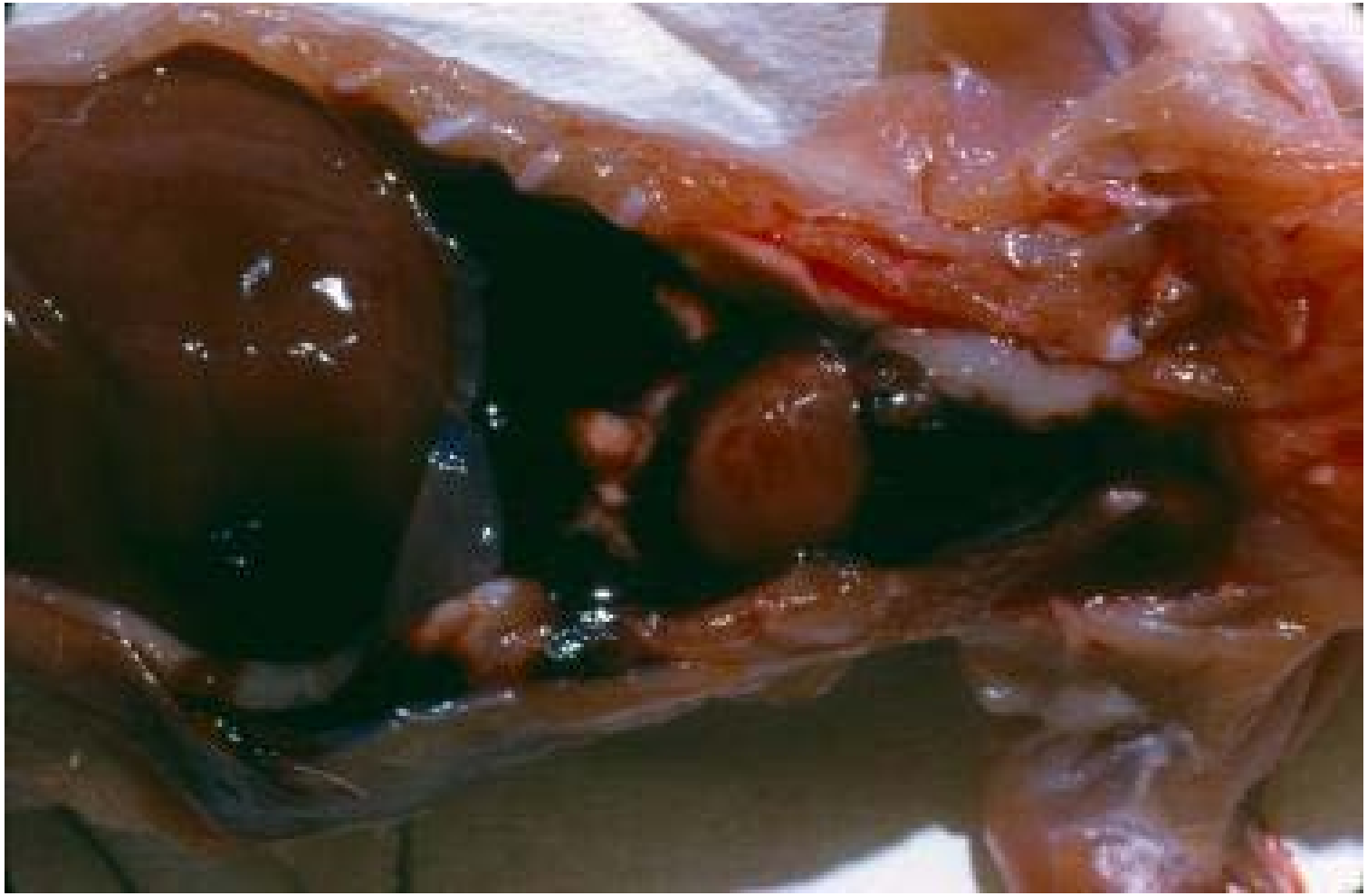
- **Intracavital, not serosal bleeds**
  - ***Factor deficiencies*** → **cavital bleeding** (hemothorax, hemoabdomen, coughing blood, bleeding into lungs, pericardial effusion)
  - ***Thrombocytopenia or platelet clumping*** → **mucosal and subdermal bleeding** (melena, petechiae, ecchymoses)

Radiographs of clinical LAAC



http://www.boulesdefourrure.fr/

LAAC post mortem



http://vettechpride.tumblr.com/

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 K 1 if needed

OR

- Option #2—Prophylactic Vitamin K
  - Decontamination + activated charcoal + Vitamin K_1 X **30 days**
    - No need to check PT while on Vit K_1
    - Give orally only
  - Recheck PT 48 hours after last dose of Vit K_1 therapy!
    - If prolonged, repeat X 2 weeks; repeat PT 48 hrs after last dose.

Bromethalin

Bromethalin

- Bromethalin vs. brodifacoum vs. bromadiolone?

- METHAMPHETAMINE addict

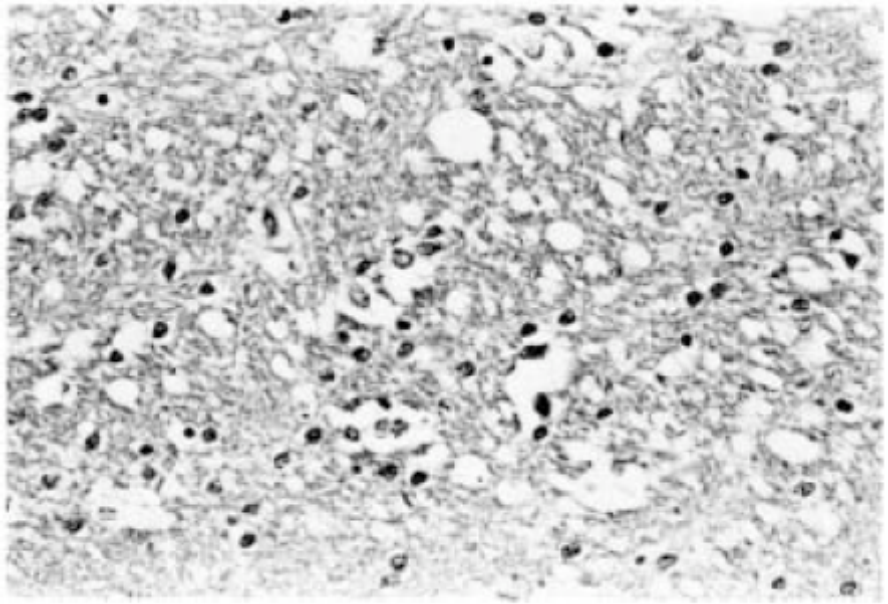
- Central nervous system (CNS) signs!

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 → ↑intracranial pressure → neurological disturbances → paralysis or convulsions → DEATH



Diffuse spongiosis of cerebral cortical white matter from a dog given bromethalin (6.25 mg/kg) 40 hours earlier.
From Dorman et al., *J Vet Diagn Invest*., 2:123-128, 1990.

Toxic Syndromes in Cats and Dogs

Paralysis
(any toxic dose)

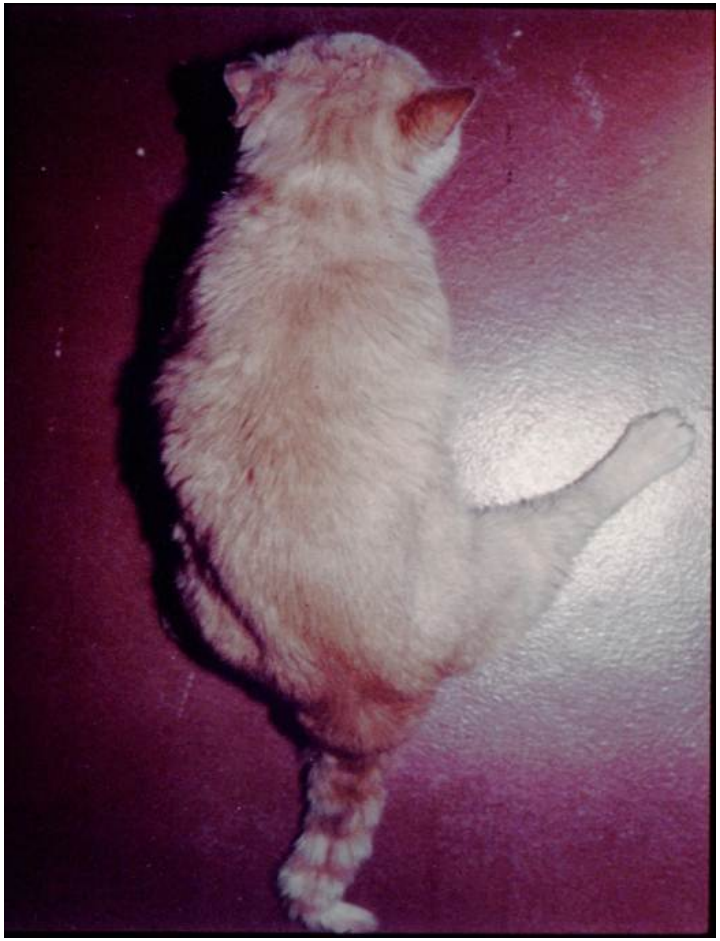
Paralysis
(toxic dose < LD50)

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

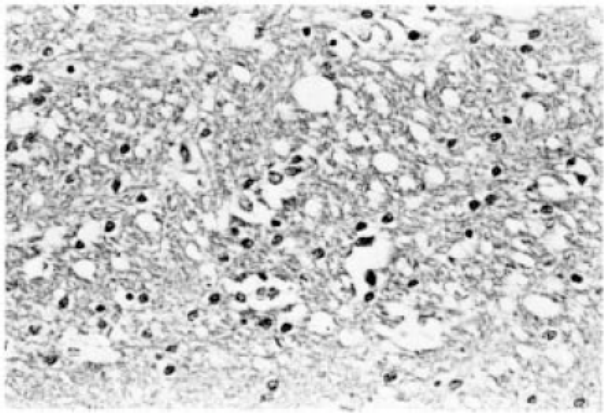


Rear limb ataxia with decreased conscious proprioception in a cat 5 days after experimental dosing of 0.45 mg/kg of bromethalin.
Courtesy of Dr. David Dorman, NCSU.

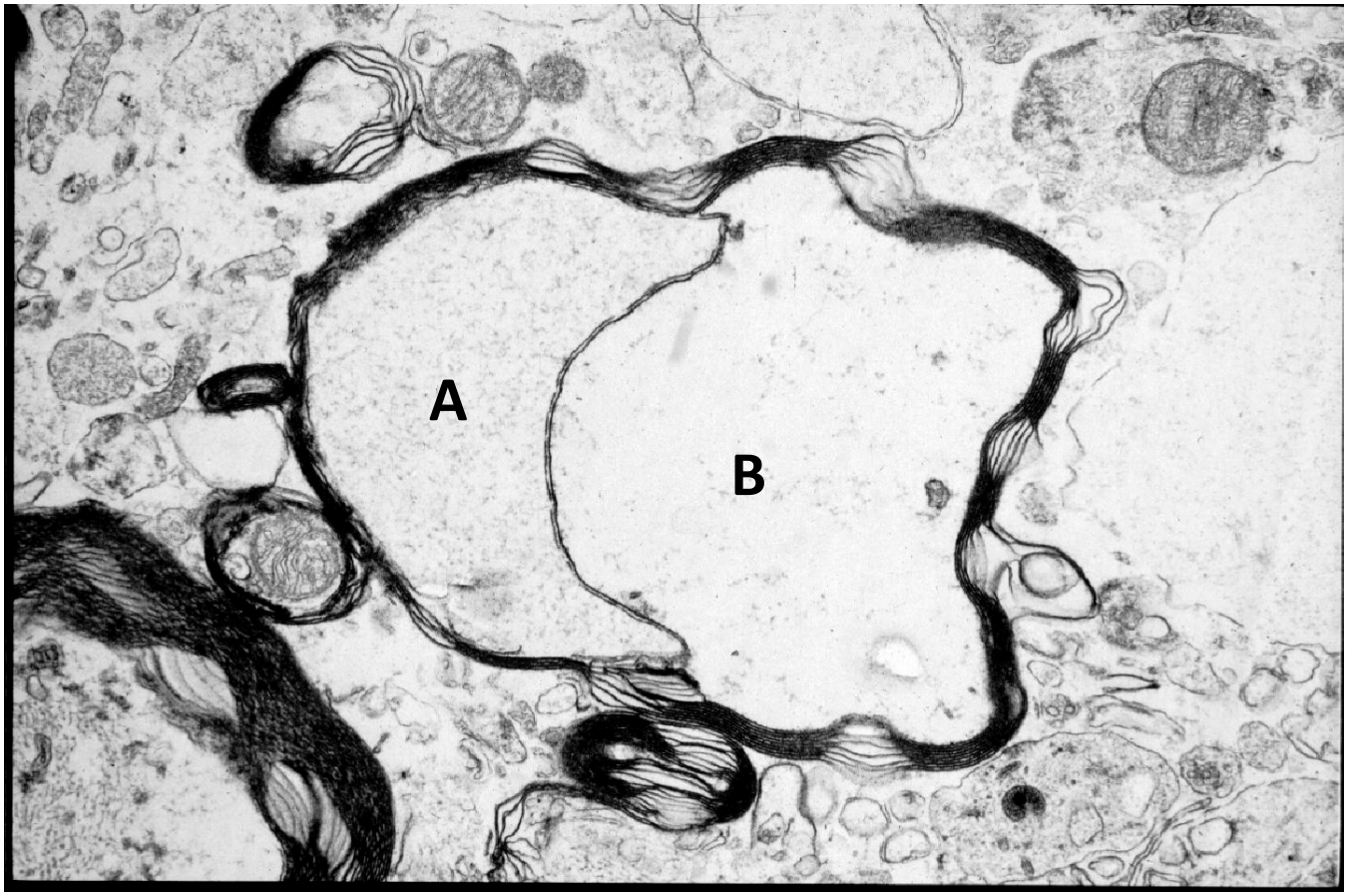
Experimental bromethalin intoxication in a cat. Animals placed on their back exhibit extensor rigidity (left image) and a lack of conscious proprioception (unable to place their feet appropriately) (right image) of all four limbs.

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

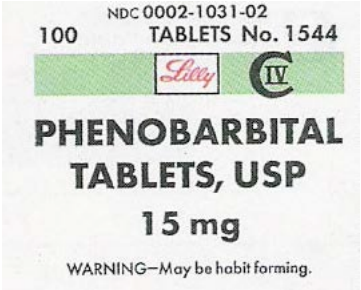
- Early and aggressive decontamination
  - Emesis or gastric lavage
  - Activated charcoal, repeated doses due to enterohepatic recirculation – check Na with sudden onset signs

- 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

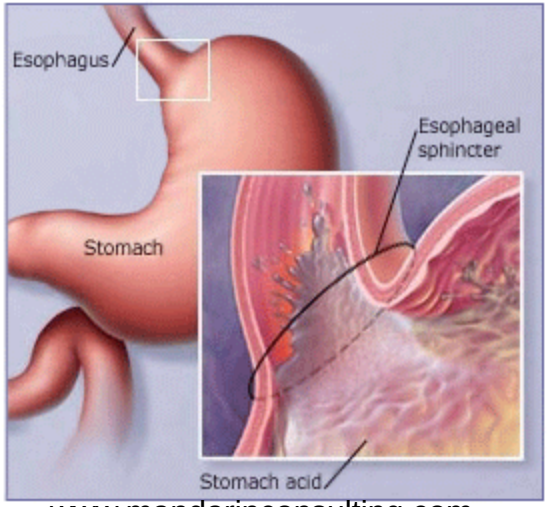
- Thermoregulation
  - Keep cool vs hot

ONCE-DAILY Cerenia™ maropitant citrate

Zinc Phosphide

Toxic Dose

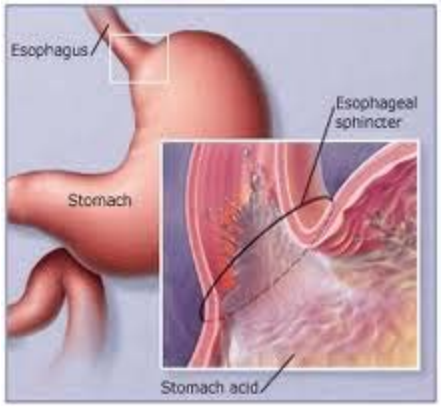
- Mole & gopher bait
- Canine LD_{50} = 20-50 mg/kg
  - Reports of surviving 300 mg/kg
- Toxicity increases in presence of gastric acid.



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



www.mandarinconsulting.com

Clinical Signs

- GI

  Vomiting, diarrhea, anorexia, abdominal pain

- CNS

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

Gray SL, Lee JL, Hovda LR, Brutlag AG. Zinc Phosphide toxicosis in Dogs: 362 cases 2004-2009. JAVMA, 2011;239:646–651

Clinical Signs

- Cardiovascular
  - Tachycardia, shock
- Respiratory
  - Tachypnea, pulmonary edema

Gray SL, Lee JL, Hovda LR, Brutlag AG. Zinc Phosphide toxicosis in Dogs: 362 cases 2004-2009. JAVMA, 2011;239:646–651

Treatment

- DO NOT FEED!
- Decontamination
  - Emesis
    - In a well ventilated area
    - Consider liquid antacid prior or lavage with 5% $NaHCO_3$
  - Activated charcoal?

- IV fluids
- Symptomatic and supportive care
  - Anti-emetic therapy

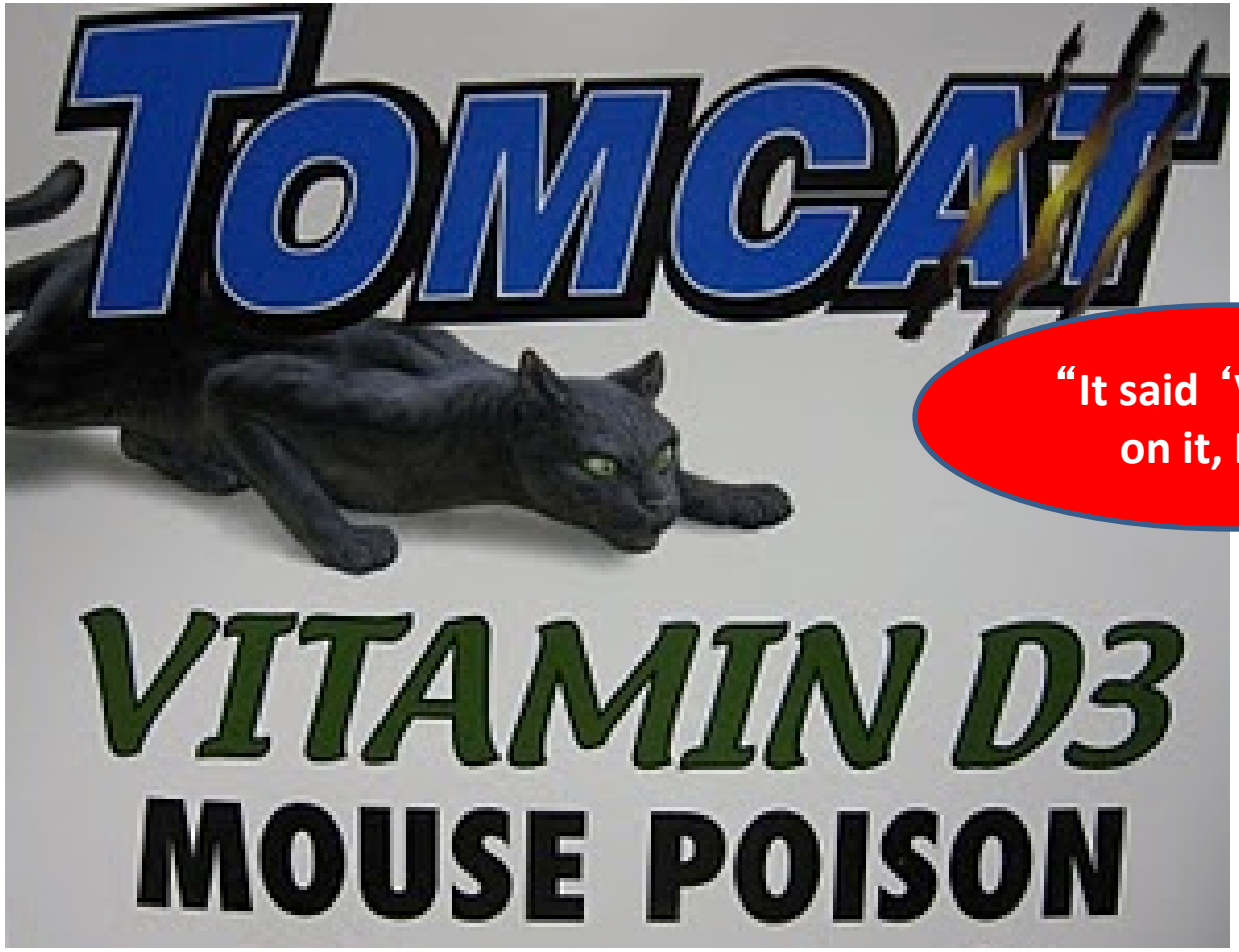
Public Health Risk

- Exposure associated with patient emesis

- Inhalation of phosphine gas reported to cause
  - Nausea
  - Headaches

http://www.thecontrarianmedia.com/2010/04/gas-masquerade/gas-mask/

Cholecalciferol



"It said 'Vitamin' on it, Doc!"

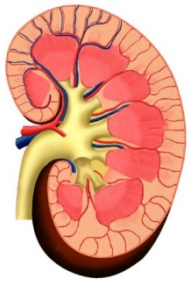
Cholecalciferol (Vit D3)

- 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, hematemesis, and dehydration
- Progression to acute renal failure (and chronic)

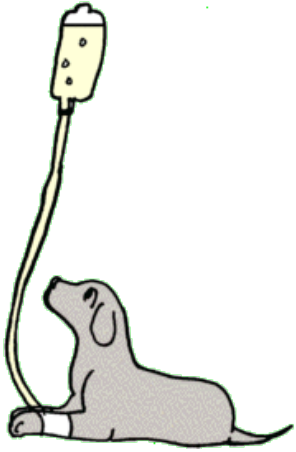
Diagnosis

- Within 12-24 hours:
  - ↑ P > 8.0 mg/dL (w/in 12-24hrs)
  - ↑ P often earlier than Ca
- Within 24-36 hours:
  - ↑ Ca > 12.5 mg/dL
- Within 24-48 hours:
  - +/- ↑ BUN/creatinine
- Monitor labs q 12 - 24hrs
- Vitamin D panel
  - PTH, ionized calcium, and 25-hydroxyvitamin D

Cholecalciferol

Must treat aggressively!

Treatment



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

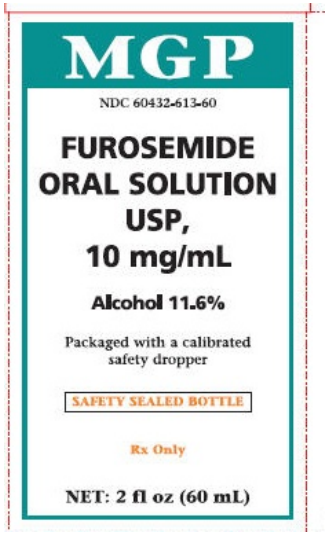
- IV Fluids
  - 0.9% NaCl diuresis for days!
  - Promotes calciuresis

Treatment

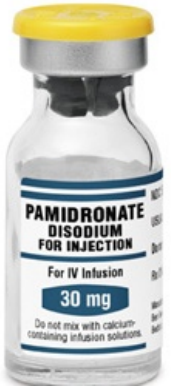
- Gastrointestinal support:
  - Phosphate binders
  - Antiemetics
  - H_2 blockers
  - Sucralfate

- 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 indirection 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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Date: June 10, 2014

FOODS TOXIC TO PETS
Date: October 7, 2014

TEACHING MOMENTS IN TOXICOLOGY
Date: December 2, 2014

ALL WEBINARS WILL BE GIVEN AT AND PRESENTED BY:

TIME: 12:00-1:00PM CENTRAL TIME (1:00-2:00PM EASTERN)

SPEAKER: AHNA BRUTLAG, DVM, MS, DABT, DABVT

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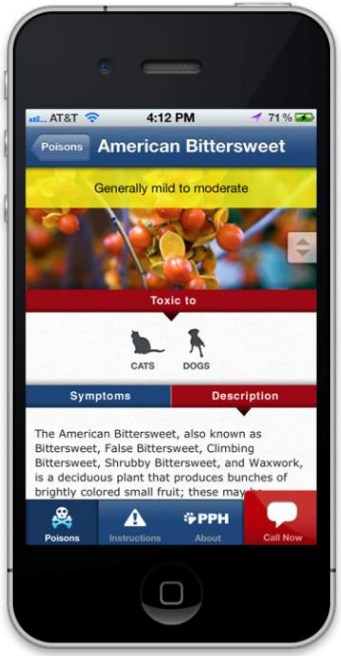

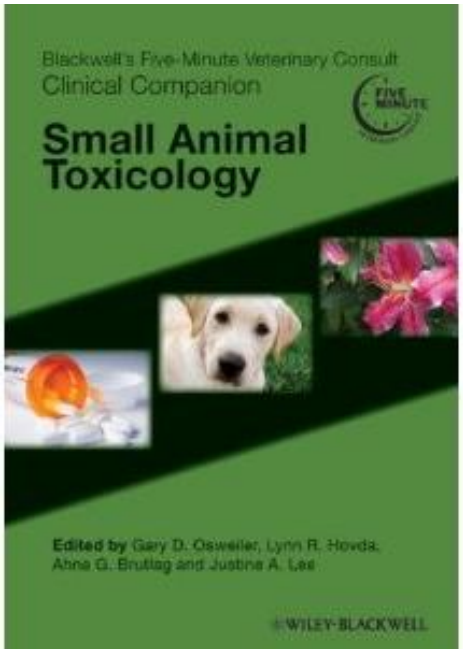

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