VET 433A Rodenticides

Sources	Anticoagulant	Bromethalin	Cholecalciferol (Vit. D_3)	Strychnine
Examples	<u>First Generation</u> Warfarin (prototype, D-CON) Diphacinone (Tomcat, Ramik, Mousemaze) Chlorophacinone (Rozol) <u>Second Generation</u> Brodifacoum *most commonly sold and highly toxic Bromadiolone Difethialone Difenacoum	Available since 1985 Kills rodents resistant to anticoagulant rodenticides Marketed in 0.01% formulation which equates to 2.84 mg / ounce of bait Comes in bait pellets, bars, and soft forms Cannot be distinguished from other rodent baits by color or appearance alone	Variety of trade names Contains active ingredient at 0.075% Vitamin D analogues can be found in human medications Dovonex or calcipotriene [an analogue of 1,25-$(OH_2)D_3$]	Alkaloid obtained from *Strychnos nux-vomica* Generally is restricted, use rodenticide (RUP)
Relevant ADME	A: Slow but complete D: highly bound to plasma proteins, especially albumin E: Various rates depending on the compound; major route is via feces but some is likely eliminated via the urine and milk Plasma $t_{1/2}$ for brodifacoum in dogs is 6 days vs 14 hours for warfarin	A: rapid absorption, peak plasma concentrations are achieved in about 4 hours M: Undergoes N-demethylation in the liver to form desmethylbormethalin, which is likely the major toxic metabolite E: Slowly eliminated; it's plasma half-life in rats is ~ 6 days Parent and metabolite are lipophilic	A: Calcifediol has a long half-life Calcitriol has a shorter half-life	A: Rapid absorption Significant % is eliminated as parent compound in the urine

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		Excretion occurs mainly in bile Enterohepatic recirculation is likely		
Toxicity	*See chart below notes	Dogs LD_{50} = 2.38-5.6 mg/kg but deaths have been reported in doses as low as 1 mg/kg Cats LD_{50} = *more sensitive* with lethal dosages of about 0.54 and 0.4 mg/kg Can show signs as low as 0.24 mg/kg and 0.75 mg/kg is uniformly fatal	Can occur in dogs with dosages as little as 0.1 to 0.5 mg/kg Oral LD_{50} (dog) = 85 mg/kg Calcipotriene/calciptriol = 50 ug/kg (tiny!) Younger animals seem to be more sensitive Cats> dogs Birds are resistant	Dogs 0.75 mg/kg b.w. is a lethal dose Steep dose-response curve
MOA	Interference with Vitamin K Delayed effect Clotting factors already in circulation are not affected Clinical coagulopathy “lag time” is between 2 and 5 days post-ingestion Can be as short as 36h depending on dose ingested	Target organ = Brain Uncouples oxidative phosphorylation leading to decreased cellular ATP production and Na^+/K^+ ATPase pump failure Loss of osmotic control due to intracellular Na^+ retention and 2 degree water retention Metabolite desmethylbromethalin is 2 to 3x more potent	Target organs = renal, cardiovascular, GI, Neurologic Metastatic tissue calcification occurs when serum calcium x phosporous is high	Competatively and reversibly antagonizes the inhibitory neurotransmitter, glycine, in the spinal cord and brainstem -exaggerated reflex stimulation -Since extensor reflexes are more powerful, limb rigidity is a result
Clinical Signs	Site, volume, and rate of hemorrhage <u>Early</u> Lethargy, depression, anorexia, dyspnea	<u>Dogs</u> <LD_{50} Paralytic syndrome beginning with hindlimb weakness and ataxia	Anorexia Vomiting Diarrhea	Rapid onset after ingestion Anxiety, stiffness, “saw-horse” stance

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	Mouth bleeding, bloody feces, epistaxis coughing <u>Advanced signs</u> Hematomas at traumatized areas Irregular heart rate, weak pulse Ataxia, convulsions (cerebral hemorrhage) Sudden death is possible	Progressive up to 2 weeks Death due to respiratory failure Recovery over several weeks <u>Cats</u> Paralytic syndrome irrespective of dose ingested Abdominal distention, ileus, and inability to urinate Prior to death > cerebrate posture	Polyuria/Polydipsia (high Ca – vasopressin – decrease ability to concentrate urine) ECG changes *Rapid onset of clinical signs dependent on form ingested Ca^{2+} > 11.5 mg/dL iCa^{2+} > 6.5 mg/dL ^Phosphorous ^BUN and Creatinine USG is hyposthenuric	Sensitive to stimuli Rigidity inhibits respiration leading to apnea Periods of relaxation become less frequent Death from anoxia and exhaustion
Diagnosis	History Clinical signs CBC/Chem/Radiographs First elevated PT Second elevated aPTT Detection of anticoagulants in baits, serum, liver or GI contents are only useful in recent exposures	No typical clinical laboratory abnormalities Detection of metabolite (desmethylbromethalin) postmortem descending order -Fat -Brain -Liver and baits Antemortem: serum	Testing calcifediol in serum Postmortem examination	Clinical signs Analysis of GI contents, liver, or urine for strychnine
Lesions	Generalized hemorrhage (especially in the thoracic and abdominal cavities) Pulmonary hemorrhage Hemorrhage in the heart Hemorrhage in the GIT Liver necrosis due to anemia and hypoxia	Postmortem lesion in the brain can help confirm, but the absence of lesions does not rule out toxicosis!	Calcium deposits	
Treatment	<u>Asymptomatic</u>	Decontamination (see chart below)	Decontamination	Early: Decontamination

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	Induce vomiting if caught within 1-2 hours Decontamination with activated charcoal and cathartic Vit. K therapy* if decontamination was incomplete Evaluate clotting factors within 24-48 hours and again at 72-96 hours post-exposure <u>Symptomatic</u> Emergency! Provide clotting factors via fresh frozen plasma If low PCV give whole blood or a pRBC transfusion O_2 therapy may be needed Vit K_1 therapy* ICU observation until p is stabilized Cage rest	Control CNS signs -Diazepam or barbiturate -Methocarbamol -Diuretics, mannitol -Lipid emulsion Prognosis is poor	Monitor serum Ca^{2+} if asymptomatic Hypercalcemic animals -Normal saline IV -Furosemide -Corticosteroids (prednisolone) -Bisphosphonates (antidote) -Phosphate binders (aluminum hydroxide)	-caution with the use of emetics due to the rapid onset of rigidity Pentobarbital, diazepam, methocarbamol Maintain airway, provide O_2 respiratory support Fluids to maintain urine output Quite environment!
Random Factoid	Sale of these in CA is widely restricted as of Jan 1st 2025 *Warfarin is still effective human thrombotic Rx rarely sold as rodenticide due to resistance			

Rodenticides are #7 on the top ten toxins ASPCA list

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Anticoagulants Toxicity Acute Oral LD_{50}

Active ingredient	Bait concentration (ppm)	Dogs (mg/kg)	Cats mg/kg)	Bait Dog (oz/lb)
Warfarin	250	20-300	5-30	1.3
Brodifacoum	50	0.2-4	25*	0.06
Bromadiolone	50	11-15	>25*	3.5
Chlorophacinone	50	?	?	?
Diphacinone	50	0.9-8	15	0.3

*Vitamin K_1 therapy

Initially give 2.5 mg/kg via SQ injection then 2.5-5 mg/kg/day po for 3-4 weeks if long-acting

Anticoagulant Rodenticide Toxicity in Lactating and Pregnant Animals

- Conservative approach
    - Wean pups and kittens early
    - Provide vitamin K_1 to pups and kittens for 2-3 weeks
    - Treat bitch or queen with vitamin K_1depending on evidence of coagulopathy
- Alternative option
    - Do not wean pups/kittens
    - Treat bitch or queen directly while monitoring the coagulation status of the pups/kittens

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Bromethalin Ingestion Decontamination Recommendations per ASPCA APCC

TABLE Decontamination Recommendations for Bromethalin Ingestion

DOSE INGESTED (MG/KG)	TIME SINCE EXPOSURE	ACTION
DOGS		
0.1–0.49	< 4 H	Emesis or 1 dose activated charcoal
	> 4 H	1 dose activated charcoal
0.5–0.75	< 4 H	Emesis + activated charcoal Q 8 H for 24 H (3 doses total)
	> 4 H	Activated charcoal Q 8 H for 24 H (3 doses total)
> 0.75	< 4 H	Emesis + activated charcoal Q 8 H for 48 H (6 doses total)
	> 4 H	Activated charcoal Q 8 H for 48 H (6 doses total)
CATS		
0.05–0.09	< 4 H	Emesis or 1 dose activated charcoal
	> 4 H	1 dose activated charcoal
0.1–0.3	< 4 H	Emesis + activated charcoal Q 8 H for 24 H (3 doses total)
	> 4 H	Activated charcoal Q 8 H for 24 H (3 doses total)
> 0.3	< 4 H	Emesis + activated charcoal Q 8 H for 48 H (6 doses total)
	> 4 H	Activated charcoal Q 8 H for 48 H (6 doses total)

Table information based on ASPCA APCC recommendations for bromethalin ingestion

Brief Vitamin D Review

Vitamin D_2 – Plant-derived form

Vitamin D3 – Animal Derived form (cholecalciferol)

25-monohydroxy vitamin D_3 (calcifediol or calcidiol)

1,25-dihydroxy vitamin D_3 (calcitriol)

Vitamin D_3 analogues (calcipotriene or calcipotriol)