

# COMMON TOXICOLOGICAL STATES OF NEONATES

**Division of Veterinary Medicine  
FVSc & AH, SKUAST-J, R.S. Pura, Jammu 181102**

# INTRODUCTION

## **Toxicant**

- A poison or poisonous agent; an intoxicant; any solid, liquid or gas that, when introduced into or applied to the body, can interfere with the life processes of cells or the organism by its own inherent qualities (toxicity) without acting mechanically and irrespective of temperature.

## **Toxin**

- A poisonous material that is synthesized or derived from an animal or plant; also referred to as a *biotoxin*. Zootoxins, bacterial toxins, and phyto (or plant) toxins are subcategories of toxins.

## **Toxicity**

- The poisonous characteristics of a substance; the degree to which something is poisonous.

## **Acute Toxicity**

- Intoxication that results from the effects of a single dose or multiple doses of a toxicant given during a 24 – hour period (e.g., dog got into a box of chocolates or dog was left in a room contaminated by chemical fumes overnight).

## **Subacute Toxicity**

- Exposure to multiple doses of a toxin or toxicant given for greater than 24 hours but no longer than 30 days (e.g., animal owner administers ibuprofen to dog for a week).

## **Sub-chronic Toxicity**

- Repeated or continuous exposures to toxicants for a duration of 1 to 3 months (e.g., patient on weekly chemotherapy for cancer).

## **Chronic Toxicity**

- Intoxication that results from prolonged exposure, with the duration of exposure being 3 months or longer (e.g., repeated exposure of a cat to low levels of lead as a result of environmental contamination and grooming of contaminated paws or hair).

## **Dose**

- The quantity of drug or toxicant administered at one time irrespective of body weight.

## **Dosage**

- The regimen governing the size, amount, frequency, and number of doses of a therapeutic agent to be administered to a patient.

## **Lethal Dose ( LD )**

- The lowest dose that causes death. An LD can be expressed
- as a percentage of individuals dying (e.g., an LD<sub>10</sub> , or, most commonly, an LD<sub>50</sub> )

## **Median Lethal Dose ( LD<sub>50</sub> )**

- The quantity of an agent that will kill 50% of the test subjects to which it is administered.

## **Hazard (Risk)**

- The likelihood that a chemical will cause harm under certain conditions. The hazard can vary for the same chemical. For example, the hazard or risk of intoxication is greater if a potentially toxic product or chemical is not stored properly and thereby the chance for accidental exposure is increased due to greater accessibility.

- 
- Poisons can be classified based upon the organ systems that are primarily affected (e.g., hepatotoxicants, neurotoxicants, nephrotoxicants, etc.).

- Animals are exposed to potentially toxic products every day, yet the actual incidence of poisoning in animals is relatively low when compared to other causes of illness, such as
  - infectious
  - metabolic diseases
  - allergy
  - trauma
  - neoplasia etc.
- Animals presenting with signs that pet owners may suspect are related to poisoning need to be fully evaluated in order to rule out the possibility of an unrelated illness.
- Dogs are inquisitive creatures with a propensity for investigating the world with their mouths, which makes it easy to understand why dogs far outrank other species in reports of exposures to potentially toxic agents.
- There is no gender predisposition to poisoning exposures, with males and females being equally represented.

(Gwaltney-Brant 2007)

- 
- Labrador retrievers, are considered to be more “poison - prone ” than others, and a review of over 68,000 animal poison control center cases involving purebred dogs showed that cases involving Labrador retrievers were three times higher than the next most common breed.

(Gwaltney - Brant 2007)

- Unlike dogs, cats have discriminating habits and appetites, making them less likely to ingest things that are not good for them.



# TOXICITIES

➤ Chemical toxicities

➤ Topical toxins

# ALUMINUM

- Al and Al-based compounds are used for a variety of purposes, from medicines such as
  - antacids
  - buffered analgesics
  - antidiarrheal agents and
  - anti-ulcerative agents
- Al is a component of beverage cans, pots and pans, siding and roofing materials and foil. It is also found in products such as antacids, astringents, buffered aspirin, antiperspirants, toothpaste and food additives.
- Poisoning in animals by Al is rare, but in several incidents the outcome has been very serious or deadly.
- Among all Al compounds, Al phosphide is of major concern to animals, because at a low stomach pH, phosphide converts to toxic phosphine ( $\text{PH}_3$ ) gas. Al has been widely studied for its toxicological effects, especially for neurotoxicity, developmental and neurobehavioral toxicity in laboratory animals.

- Aluminum (Al) has a predilection for the brain and nervous tissues, therefore it touches every organ in the body via its nerve connections. The implication of Al in the etiology of a neurodegenerative disease like Alzheimer's has been well studied, and its effects at the nuclear, cytoplasmic, cytoskeletal, membrane, synaptic and neurotransmitter levels have been well studied.

(McLachlan, 1995; Savory *et al.*, 2006; Krewski *et al.*, 2007; Garcia *et al.*, 2010)

- In dogs, chronic Al exposure and its toxicity is linked to Cognitive Dysfunction Syndrome (CDS) or Doggie Alzheimer's Syndrome. Sometimes, a similar syndrome is observed in cats. These animals exhibit memory loss and personality change, and finally they fail to recognize their owners.

- Since Al readily crosses the blood–brain barrier and the placental barrier, it appears that neurotoxicity and developmental toxicity are of particular concern in relation to Al toxicity.

(Gupta, 2009; Kumar and Gill, 2009; Domingo, 2011)

# Pathogenesis

CNS AND SKELETAL SYSTEM ARE MAJOR TARGET ORGANS OF Al

Al ingestion

Neurodegenerative disease  
(Alzheimer's, encephalopathy, amyelotropic sclerosis)

Deposits in Hippocampus, cortex, amygdala

Rich in glutameric receptors & transferrin receptors

Alteration in detoxification of ammonia

Neuronal Death

Displaces cations (Ca, Mg, Fe)

Alteration in Neurotransmitter release

Modify cholinergic neurotransmission

Al competes with Mg in biological system binds to transferrin and citrate

- ✓ Acute poisoning of Al in animals is rare, but a high acute dose or repeated long-term exposure can lead to serious toxicological effects.
- ✓ Toxicity of Al depends on its chemical form, route of exposure and animal species.
- ✓ Oral LD<sub>50</sub> values for Al nitrate in Sprague-Dawley rats and Swiss Webster mice are reported to be 261 and 286 mg Al/kg, respectively. For Al bromide, these values are 162 and 164 mg Al/kg, respectively.

(Llobet *et al.*, 1987)

# CLINICAL SIGNS

In dogs, the signs of Al toxicity may include

- ✓ Dermatitis,
- ✓ Coryza
- ✓ Nasal discharges,
- ✓ Loss of black pigment on the nose pad,
- ✓ Aggressive Violent behavior.

Marked signs of neurotoxicity, including

- ✓ Ataxia,
- ✓ Splaying and
- ✓ Dragging of hind limbs, and
- ✓ Paralysis

Toxic effects of Al depend on the target organ. Such effects may in part be related to Al deposition and substitution of physiological elements, such as calcium, magnesium and iron.

Alterations by Al deposits can occur in:

- ❖ Bone
- ❖ Interfering in heme synthesis leading to anemia
- ❖ Myocardium, leading to myocardial infarction
- ❖ Brain, leading to neurotoxicity and cognitive impairment.
- ❖ In addition, Al can cause hepatic and renal dysfunction and osteoarthritis.
- ❖ Al crosses the placental barrier, accumulates in fetal tissues and produces embryo/fetal toxicity, birth defects and developmental and neurobehavioral toxicity.

Chronic exposure to Al results in an increase in Al levels in bones, and this may result in bone abnormalities including reduced bone formation and demineralization, or even osteoarthritis. Osteomalacia is observed in dogs.

## Diagnosis

Diagnosis of Al poisoning can be based on a history of Al

- ✓ Exposure,
- ✓ Clinical signs and
- ✓ Confirmation of Al in animal tissues.

Using an Atomic absorption spectrometer or an inductively coupled plasma, Al can be measured in tissue, blood, urine, feces and hair. Only urine measurement can indicate whether recent exposure to excess levels of Al has occurred.

## TREATMENT

There is no specific antidote for acute Al toxicity.

So, treatment relies upon symptomatic and supportive therapies.

- ✓ Use of activated charcoal and cathartics can be rewarding.
- ✓ In the case of Al phosphide, sodium bicarbonate (5% solution) can be administered to stop conversion of phosphide to phosphine gas.
- ✓ There is evidence that dietary Silicone (Si) can reduce gastrointestinal Al absorption and increase its elimination.
- ✓ Dietary Si can also reduce brain Al accumulations.
- ✓ In the case of chronic exposure to Al, chelation therapy with deferoxamine or 3-hydroxypyridine-4-ones is very effective.

# PETROLEUM DISTILLATES AND OTHER ALIPHATIC HYDROCARBONS

## Sources

Kerosene, gasoline, and mineral seal oil are prototypical hydrocarbons.

Hydrocarbons are found in

- ✓ Lubricants,
- ✓ Degreasers,
- ✓ Waxes,
- ✓ Varnishes,
- ✓ Cleaning fluids,
- ✓ Lamp oil

## Signs

Most commonly the pulmonary system, CNS and GI system are involved: -

- ✓ Some animals emit a characteristic hydrocarbon odor, and many develop vomiting, diarrhea.
- ✓ Hepatotoxicity, renal toxicity, and cardiac arrhythmias may also occur.
- ✓ Aspiration, and chemical induced pneumonitis are common after exposure.
- ✓ Cough
- ✓ Hyperthermia
- ✓ Dyspnea
- ✓ Cyanosis

## Management

- ✓ Oxygen and positive end-expiratory pressure therapy.
- ✓ For dermal contamination with thick tarry or asphalt materials, mild detergents and fur clipping is most useful

# NAPHTHALENE

## Source

Primary source is moth balls

## Signs

- ✓ Vomiting
- ✓ Lethargy
- ✓ Seizure

There is Hemolytic anemia and Heinz body formation, methemoglobinemia, hemoglobinuria, and renal failure

## Management

Rx is largely based on GI decontamination and supportive care (i.e., fluid therapy, warming, control of methemoglobinemia with methylene blue until recovery)

M  
E  
C  
H  
A  
N  
I  
S  
M

Naphthalene



1,2-naphthoquinone and 1,4-naphthoquinone



Redox Cycling And Oxidative Stress.

Protein denaturati  
on

Lipid peroxidation, glutathione depletion

Contributing to the toxic manifestations of naphthalene. Glial cell damage

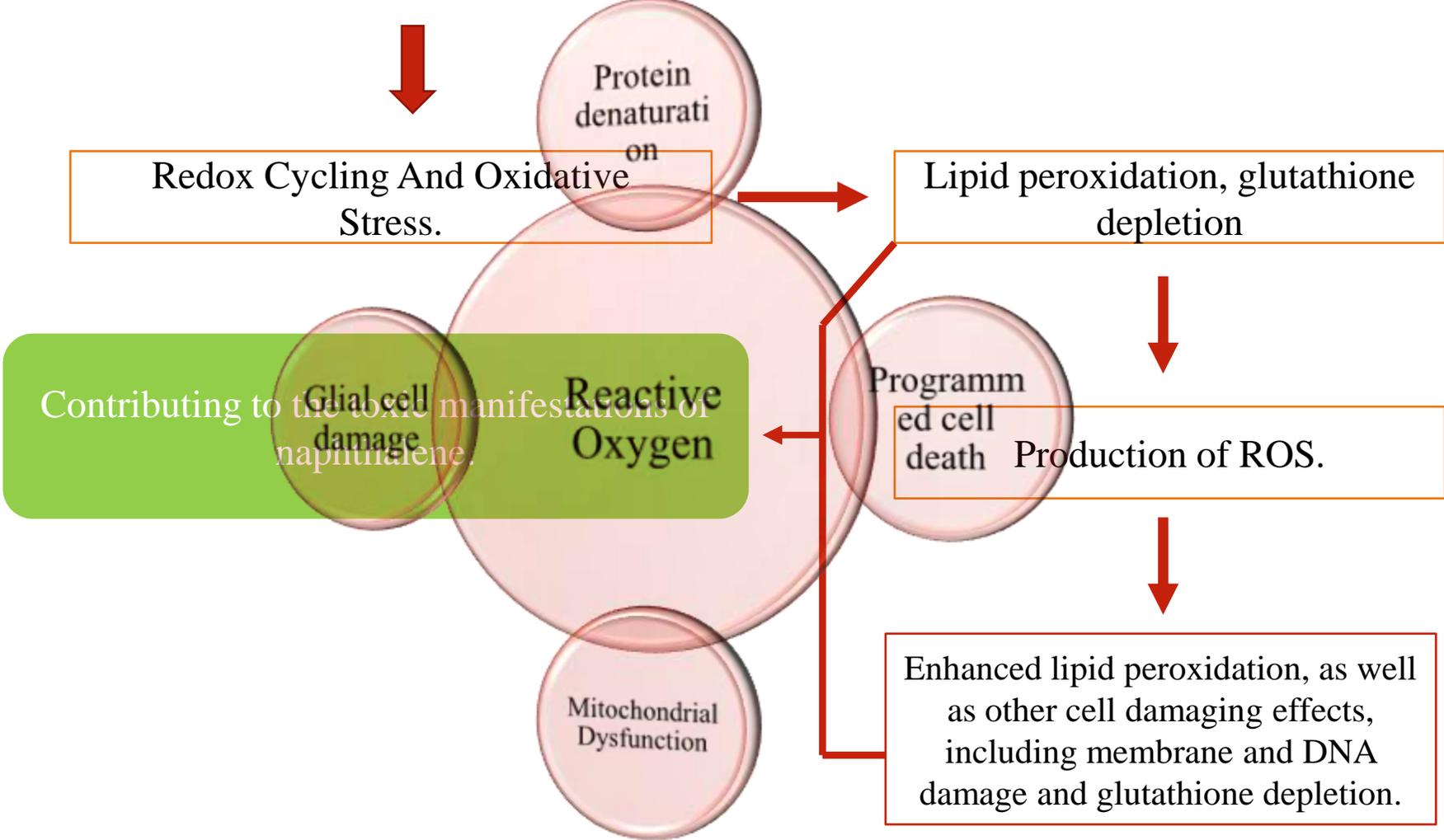
Reactive Oxygen

Programmed cell death

Production of ROS.

Mitochondrial Dysfunction

Enhanced lipid peroxidation, as well as other cell damaging effects, including membrane and DNA damage and glutathione depletion.



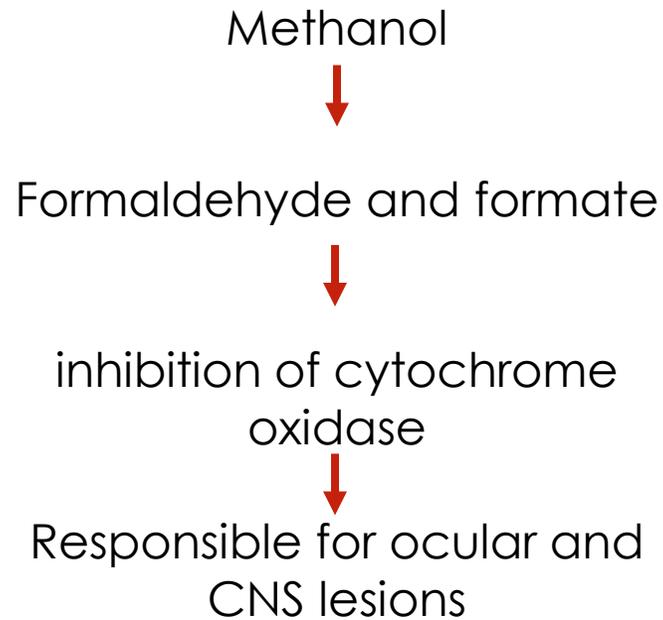
## Methanol ( wood alcohol)

### Sources

Methanol based automotive windshield fluid, antifreezes and related consumer products.

Oral lethal dose of methanol in dogs is 4-8 mg/kg

### Pathogenesis



### Signs

Intoxication develops within 1 hour of ingestion and may result in

- ✓ CNS depression
- ✓ Behavioral changes ( vocalization, excitability)
- ✓ Ataxia
- ✓ Hypothermia
- ✓ Respiratory or Cardiac arrest

Rx :- Based largely on GI decontamination and supportive care ( fluid therapy, warming, assisted ventilation until recovery)

# ANTICOAGULANT RODENTICIDES

## Diagnosis

Significant prolongation of

- ✓ Activated clotting time
- ✓ Prothrombin time
- ✓ Activated partial thromboplastin time (aPTT)
- ✓ Elevated levels of carboxylated forms of V-K dependant coagulation factors

## Treatment

- V-K<sub>1</sub> is antidotal with oral dose of 2.5 to 5 mg/kg q8-12h for 2-4 weeks depending upon whether the ingested anticoagulant was a short or long acting agent
- Synthesis of new C.F takes at least 12 hours.
- In the term clinically ill patients may need life support measures (whole blood, fresh-frozen plasma transfusion) to prevent further blood loss

## Signs

Typically signs develop within 2-5 days after exposure and may vary depending upon site and volume of blood loss.

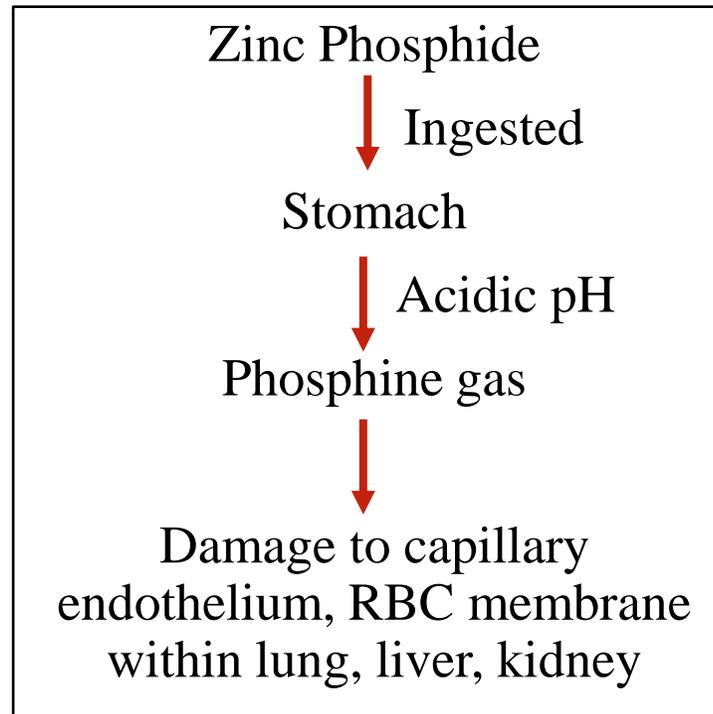
- ✓ Petechiae & ecchymosis of skin and M.M
- ✓ Hematoma
- ✓ Weakness
- ✓ Pallor
- ✓ Respiratory distress
- ✓ CNS depression
- ✓ Hematemesis
- ✓ Epistaxis
- ✓ Melena
- ✓ Ataxia
- ✓ Paresis
- ✓ Seizures
- ✓ Sudden death

# Zinc Phosphide

## Source

- ✓ Zinc phosphide is a rodenticide
- ✓ Lethal dose is 20-50 mg/kg

## Pathogenesis



## Signs

- ✓ Anorexia
- ✓ Lethargy
- ✓ Weakness
- ✓ Abdominal pain
- ✓ Vomiting occurs within 1-4 hours

Signs may progress to

- ✓ Recumbency
- ✓ Whole body tremors
- ✓ Seizures
- ✓ Cardiopulmonary collapse
- ✓ Death

## Management :-

No specific antidote exists, however supportive therapy including antacids (containing Mg & Al hydroxide) is considered beneficial.

Sodium bicarbonate can be given orally to stop liberation of phosphine gas

# Cholecalciferol (VITAMIN D)

## Treatment

- ✓ GI decontamination soon after ingestion
- ✓ Increase renal clearance of Ca via furosemide admin @ 5 mg/kg IV fwd by 2.5 mg/kg PO TID in combo with fluid therapy (Isotonic Saline Solution 2c)
- ✓ Prednisolone @ 2-3 mg/kg PO OD aids in decreasing osteoclastic activity and GI calcium absorption
- ✓ Calcitonin @ 4-6 mg/kg SC every 3 hrly may aid to further reduce serum Ca conc.

Pamidronate disodium @ 1.3 to 2 mg/kg in 0.9% Saline IV has been shown to reverse V-D induced hypercalcemia. It interrupts osteoclast activity and induces osteoclast apoptosis

## Pathogenesis

Cholecalciferol and other V-D metabolites



Abnormal increase in Intestinal absorption of Ca



- ✓ Stimulation of bone resorption
- ✓ Tubular reabsorption of Ca



Persistent hypercalcemia (>12mg/dl)

- ✓ Soft Tissue mineralization may occur and when severe can be apparent radiographically.
- ✓ Death is usually due to cardiac failure, renal failure, or both

## Signs

Appear with 3-5 days after ingestion

- ✓ Anorexia
- ✓ CNS depression
- ✓ Vomiting occasionally with hematemesis
- ✓ Muscle weakness
- ✓ Constipation
- ✓ Bloody Diarrhea
- ✓ Polyuria
- ✓ Polydipsia

# ORGANOPHOSPHORUS AND CARBAMATE INSECTICIDE

## Diagnosis

Determination of reduced ChE activity in blood, brain and retinal tissues.

## Pathogenesis

OP and CM



- ✓ Reversible AChE inhibitors within nervous tissue and at the neuromuscular junction
- ✓ Responsible for the hydrolysis of the neurotransmitter ACh

## Treatment

- Life saving therapy should be given immediately.
- ✓ Atropine sulphate @ 0.1 -0.2 mg/kg to alleviate severe bradycardia and excessive bronchiolar constriction and mucus hypersecretion.
  - ✓ Prolidoxime chloride is used as AChE enzyme reactivator @ 20 mg/kg IM q12h

# LEAD

## Diagnosis

- ✓ Nucleated RBS may be found in PBS of affected dogs without evidence of severe anemia.
- ✓ Basophilic stippling is sometimes observed in RBC
- ✓ In cats, nucleated RBC and basophilic stippling is seldom found
- ✓ Toxicosis may be confirmed by chemical analysis with blood concentration  $\geq 0.20$  ppm.

## Treatment

- ✓ Calcium versenate (calcium disodium ethylenediamine tetraacetate, CaEDTA @ 25 mg/kg in DNS SC
- ✓ Succimer (Dimercaptosuccinic Acid) @ 10 mg/kg TID PO
- ✓ Thiamine Hydrochloride  
When used in combination with CaEDTA, thiamine is a valuable agent for the treatment of lead poisoning. Thiamine hydrochloride reduced the deposition of lead in most tissues, especially liver, kidney, and the central and peripheral nervous system. The recommended dose is 2 mg/kg BW intramuscularly, given at the same time as CaEDTA, with a total daily dose not to exceed 8 mg/kg BW.

# TOPICAL TOXINS

- ✓ When dealing with these types of intoxications, practitioners must protect themselves from exposure by wearing gloves.
- ✓ Washing the patients with a mild soap is adequate for most poisoning, although a degreaser may sometimes be necessary.

Toad poisoning

New generation  
insecticide

Antifungals-Zinc  
undecylenate

# TOAD POISONING

## Diagnosis

- ✓ Stress leukogram
- ✓ Mild fluid loss
- ✓ Mild elevation in serum in ALP and serum potassium concentration
- ✓ Decrease in Sodium, Phosphorus, total protein concentration.
- ✓ Digoxin serum immunoassay.

## Treatment

- ✓ Charcoal is thought to be of some benefit because some toxins enter enterohepatic circulation.
- ✓ Seizures may be controlled by diazepam, Propofol, pentobarbital.
- ✓ In severe cases cerebral edema may also occur secondary to seizure activity may need to be treated with short-acting corticosteroids, mannitol and furosemide.
- ✓ Intravenous fluid therapy within 1-2 hrs.

## Signs

- ✓ Disorientation
- ✓ Ataxia
- ✓ Stupor
- ✓ Ataxia
- ✓ Stupor
- ✓ Nystagmus
- ✓ Profuse drooling
- ✓ Brick red mucous membrane
- ✓ Mydriasis
- ✓ Cardiac arrhythmias
- ✓ Death

# NEW GENERATION INSECTICIDES

- ✓ Topical agents like fipronil, imidocloprid, lufenuron and selamectin all have wide margins of safety, but local dermatitis has been reported. These drugs have potential to cause hypersensitivity reaction.
- ✓ Mild GIT upset is seen and symptomatic therapy may be required.
- ✓ Ocular exposure is best treated with saline lavage.

## Mode of action

Fipronil



Non competitive blocker of GABA-gated chloride channels

Imidocloprid



Competitive inhibitor of nicotinic receptors in postsynaptic receptors

Lufenuron



Inhibitor of chitin synthetase

Selamectin



Inhibitor of glutamate-gate channels

## ANTIFUNGALS-ZINC UNDECYLENATE

- ✓ Sunscreen diaper rash ointments, and antifungals can all contain zinc.
- ✓ Acute ingestion of Zinc oxides usually results in a self-limiting emesis that rarely require Rx.
- ✓ Manifested by GIT disturbances, hypotension, hemolytic anemia, jaundice, pulmonary edema.
- ✓ Milk or water given orally helps reduce intestinal absorption of zinc, and calcium EDTA chelates Zinc absorbed systemically.



**Thank You**