Veterinary Toxicology

Toxicology

Definitions

Toxicology: Is that branch of pharmacology which deals with the undesirable effects of chemicals (poisons) or toxins on living systems. Or the studying of the nature, effects and detection of poisons and the treatment of poison.

Veterinary Toxicology: Is the diagnosis and treatment of poisoning in animals other than humans, particularly livestock and companion animals, but not excluding undomesticated species. Other important concerns of veterinary toxicology are the possibletransmission of toxins to the human population in meat, fish, milk, and other foodstuffs and the care and ethical treatment of experimental animals.

Poison (Toxicant): A poison (toxicant) is any substance that causes a harmful effect when administered to a living organism.

Toxin: A toxicant produced by a living organism.Generally refers to toxic substances that are produced by biological systems such as plants, animals, fungi, or bacteria. Toxin should never be used as a synonym for toxicant.

Toxicant: Toxic substances that are produced by or are a by-product of anthropogenic (human-made) activities.Thus, zeralanone, produced by a mold, is a toxin, whereas ”dioxin”, produced during the production and/or combustion of certain chlorinated organic chemicals, is a toxicant.

Xenobiotics: Foreign, natural, or man-made (synthetic) chemicals, including drugs, pesticides, environmentaland industrial agents.

Hazard (Risk): Is the likelihood that a chemical or drug will cause harm under certain conditions.

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Pollution: A contamination of soil, water, food, or the atmosphere by the discharge or admixture of poisonous materials.

Pollutant:-Asubstance which occurs in the environment (air, water, soil) Possibly by human activity and adversely affectsthe living organism who live in this environment.

LD50(Lethal-Dose-50): It's the dose of a toxic agent that kills 50 % of population.

Teratogen: Any substance capable of causing malformation during development of the fetus.

Carcinogen: Any substance that causes cancer.

Mutagen: Any substance that causes alterations in cellular DNA.

Therapeutic Index (TI): The ratio of median lethal dose to median effective dose. (**LD50\ED50).**

Margin of safety: The ratio of the dosage required to kill 1% of population, compared to the dosage that is effective in 99% of population.

Minimum toxic dose (MTD):- The lowest toxic dose that cause detectable toxic effect.

Specialized Areas of Toxicology:

1. **Clinical Toxicology:** Is the diagnosis and treatment of human or animal poisoning
2. **Forensic Toxicology:** The medical aspects of the diagnosis and treatment of poisoning and the legal aspects of the relationships between exposure to and harmful effects of a chemical substance. It is concerned with both intentional and accidental exposures to chemicals.
3. **Environmental Toxicology:** This is concerned with the movement of toxicants and their metabolites in the environment and in food chains and the effect of such toxicants on populations of organisms. This understood is involving the industrial toxicology as a specified area from environmental toxicology.

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4. **Biochemical and Molecular Toxicology:**Consider events at the biochemical and molecular levels, including enzymes that metabolize xenobiotics, generation of reactive intermediates, interaction of xenobiotics or their metabolites with macromolecules, gene expression in metabolism and modes of action, and signaling pathways in toxic action.

Classification of ToxicAgents:

Toxic agents are classified according to:

1. **Target organs :**(liver, kidney, hematopoietic system, etc.).
2. **Use :**(pesticide, solvent, food additive, etc.).
3. **Source :**(animal and plant toxins).
4. **Effects :**(cancer, mutation, liver injury, etc.).
5. **Physical state :**(gas, dust, liquid).
6. **Chemical stability or reactivity :**(explosive, flammable, oxidizer) .
7. **General chemical structure :**(aromatic amine, halogenated hydrocarbon, etc.).
8. **Poisoning potential :**(extremely toxic, very toxic, slightly toxic, etc.).
9. **Basis of biochemical mechanisms of action :**(e.g., alkylating agent, cholinesterase inhibitor, methemoglobin producer).

Ranks (types or degrees) of toxicity:

We can rank the toxicity according to the dose frequency and term of exposure to the following:-

1. **Acute toxicity:**It's the toxicity produced by a chemical when it is administered in **one dose** during a period not exceeding **24 hours**.
2. **Sub-acute toxicity:**It's the toxicity produced by a chemical when it is administered in **repeated doses** during a period **less than one month**.
3. **Sub chronic toxicity:**It's the toxicity produced by a chemical when it is administered in **repeated doses** during a period **less than three months**.
4. **Chronic toxicity:**It's the toxicity produced by a chemical when it is administered in **repeated and small doses** during a period **more than three months**.

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Spectrum of Undesired Effects

The spectrum of undesired effects of chemicals is broad. Some effects are deleterious and others are not. In therapeutics, for example, each drug produces a number of effects, but usually only one effect is associated with the primary objective of the therapy; all the other effects are referred to as undesirable or side effects of that drug for that therapeutic indication. However, some of these side effects may be desired for another therapeutic indication.

Toward &Untoward Effect of Drug

Toward effect:-It's the main therapeutic or pharmacological effect of drug in the body

Untoward effect :-This is the effect that accompanied with therapeutic effect and it may be desirable or undesirable effect this include :-

1. **Secondary effect** :-Secondary pharmacological effect that accompanied therapeutic effect and consider sometimes as desirable effect .
2. **Side effect** :-Secondary predicted undesirable effect that accompanied therapeutic effect.
3. **Adverse effect** :-Unpredicted undesired effect caused by drug used at recommended doses .

For example, the "first-generation" antihistamine diphenhydramine (Benadryl) is effective in reducing histamine responses associated with allergies, but it readily enters the brain and causes mild central nervous system (CNS) depression (drowsiness, delayed reaction time).

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Table of Toxicity Rating Chart

Toxicity Rating or Class	Dosage	PROBABLE LETHALORAL DOSE FORHUMANS For Average Adult
1. Practicallynontoxic	>15 g /kg	More than 1 quart
2. Slightly toxic	5- 15 g /kg	Between pint and quart
3. Moderately toxic	0.5 – 5 g/kg	Between ounce and pint
4. Very toxic	50 – 500 mg /kg	Between teaspoonful and ounce
5. Extremely toxic	5 - 50 mg /kg	Between 7 drops and teaspoonful
6. Super toxic	< 5 mg / kg	A taste (less than 7 drops)

Factors Affecting Toxicity :

1. **Rate of Entry and Route of Exposure**: that is, how fast the toxic dose is delivered and by what means.
2. **Age :**can affect the capacity to repair tissue damaged.
3. **Previous Exposure:**can lead to tolerance, increased sensitivity or make no difference
4. **State of health, medications and physical condition :**can affect the toxic response.
5. **Pre-existing Disease :**can result in increased sensitivity.
6. **Environmental Factors** : such as temperature and pressure.
7. **Host Factors** : including genetic predisposition and the sex of the exposed individual.

Diagnosis of toxicity

The diagnosis of toxicity is difficult but proceed on four to five evidences :-

1. **Symptomatic Evidence** :-According to specific symptoms .
2. **Circumstantial Evidence** :-Searching for source of poisoning .
3. **Pathological Evidence** :- Gross & histological examination .
4. **Analytical Evidence** :-Analysis samples for determination of significant toxic amount in different organ , blood and tissue .
5. **Experimental Evidence** :-By dosing of suspected material in laboratory animal to determine toxicity .

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Steps of poisoning treatment

1. **Clinical stabilization:**by maintaining the airway, breathing and circulation.
2. **Clinical evaluation of the poisoned state:**by knowledge of the case history of the state, then doing the requested laboratory examinations.
3. **Prevention of further poison absorption:**by removing the suspected poisonous material away from the state (man or animal) by :-
   a) **First step** :- Remove the suspected material so no more will be ingested (by washing).
   b) **Second step** :- Remove any poisonous material ingested but not yet absorbed by using of **emetic** (1% copper sulphate or abomorphine) or **gastric lavage** by using (ringer lactate or saline) or **adsorbent** as charcoal .in case of ruminant by makerumenotomyfor removal of toxicant .
   c) **Third step** :- Removal of toxic material which is passed from stomach into the gut by using of **purgative** (Magnesium or Sodium sulphate) .
4. **Enhancement of poison elimination:**byalkalinization of the urine, hemodialysis, hemoperfusion, hemofiltration, plasma exchange or exchange transfusion, and serial oral activated charcoal.
5. **Using of antidotes in poisoning:**The antidotes render poisons harmless once they have been absorbed in to the body. There are not too many specific anti- dotes. The various available antidotes and their mechanisms of action are listed below:

Mechanism 1 :-*Antidote complexes with poison rendering it inert*.Examples are the heavy metals which are chelated by EDTA, and arsenic which complexes with dimercaprol (BAL).

Mechanism 2 :-*Antidote accelerates biotransformation of toxicant to a nontoxic product*.For example, antidotes nitrite and thiosulfate complex with cyanide to form cyanmethemoglobin and thiocyanate, respectively. Thiocyanate is 200 times less toxic than cyanide.

Mechanism 3 :-*Antidote blocks formation of a toxic metabolite from a less toxic parent compound.*Conversion of methanol to formic acid, and ethylene glycol to oxalic acid, respectively, by alcohol dehydrogenase is blocked by ethanol as an antidote.

Mechanism 4 :-*Antidote specifically accelerate the excretion of toxicant*.The presence of chloride in bromide poisoning or calcium in strontium poisoning aids in rapid elimination of the toxicants bromide and strontium, respectively.

Mechanism 5 :-*Antidote compete with toxicant for essential receptors*.For example, vitamin K competes with coumarin anticoagulants (e.g., warfarin) for receptors involved in formation of prothrombin.

Mechanism 6 :-*Antidote blocks receptors that are responsible for toxic effect.*Example includes organophosphate poisoning treated with atropine as an antidote.

Mechanism 7 :-*Antidote restores normal function by repairing or bypassing effect of poison*.This mechanism is illustrated by the use of methylene blue in the treatment of nitrite poisoning.

6. **Supportive treatment of the poisoned state:**by maintaining of the vital functions of the body working until the antidote neutralizes the poisonous effect.

Toxicokinetics

Absorption:Movement of the toxicant into the body from the site of administration .

Routes of Absorption :

Enteral: Oral, rectal.

Parenteral: Intradermal, subcutaneous, intravascular (intravenous, intra-arterial), intramuscular.

Cutaneous: Topical and transdermal.

Miscellaneous: Inhalation, sublingual, transmucosal, intranasal, intrathecal, intraventricular.

Rates of Absorption

Fastest-to-slowest: Intravascular > inhalation > sublingual > intranasal > intramuscular > rectal > oral > subcutaneous > topical > transdermal.

Rate of absorption: Predicts the onset of action of xenobiotics.

Extent of absorption: Predicts the bioavailability of the xenobiotic or the extent of its pharmacologic effect. Example: digoxin has 50% bioavailability.

Physiochemical Factors Influencing Absorption:

1. **Molecular weight (MW):**Low M W promotes rapid absorption by passive diffusion.
2. **Blood flow:**High blood flow favors high absorption. Example: intestinal > gastric absorption.

3. **Surface area:**High surface area favors high absorption. Example: intestinal > gastric absorption.
4. **Contact time:**Absorption is inversely proportional to gastrointestinal transit time. Example: cathartics speed transit time and limit absorption.
5. **Water solubility:**Water-soluble (hydrophilic) xenobioticscannot cross lipoprotein membranes andmust filter through aqueous channels.
6. **Lipid solubility:**Lipid-soluble (lipophilic) xenobioticsreadily cross lipoprotein membranes forincreased absorption and often enter enterohepaticcycles that decrease renal elimination.Example: Opioids: Fentanyls. From long-actingto short-acting; Carfentanil> fentanyl >sufentanil>alfentanil.
7. **Polarity:**Lack of polarity or charge favors enhancedabsorption by passive diffusion.
8. ***PH:***Acidictoxicants (ASA) demonstrate increased absorptionin the acidic stomach; basictoxicantsdemonstrate increased absorption in the alkalineintestine (jejunum > ileum*).(likedrugs, the toxicants fallow (Henderson-Hesselbach Equation)*

Methods of transport of the toxicant across cell membrane:

1. Passive diffusion (simple diffusion)depend on lipid solubility,example (weak acids,weakbasis).
2. Through aqueous pores.
3. Carrier mediated transport (facilitated diffusion).
4. Active transport.

Distribution:Movement of the toxicant from intravascular to extravascular compartment.

Factors that effect on toxicant distribution:

1. **Blood flow:**Determined by the cardiac outputand accounts for initial distribution of xenobiotics and preferentially perfuse brain, liver,kidneys > muscle > fat > bone.
2. **Toxicantstructure:**Uncharged, hydrophobic,and lipophilictoxicants readily cross lipoproteinmembranes.
3. **Protein binding:**Plasma and specialized carrierproteins sequester xenobiotics in the centralplasma compartment and often become saturated,resulting in high plasma concentrationsof unbound toxins.
4. **Physiologic barriers:**Protect downstream targetorgans from xenobiotic distribution and toxicity.Example: blood–brain barrier, placentalbarrier, blood–testis barrier.

Volume of Distribution (Vd): The theoretical volume into which atoxicantdistributes.

Determinants of the Vd:

1. Drug dose administered.
2. Drug bioavailability
3. Peak plasma concentration

Vd = amount of toxicant in the body/ toxicant concentration in plasma.

Classical Compartment Models of Distribution :

A- One-Compartment Model:Some xenobiotics rapidly enter the central circulatory compartment for rapid distribution to tissues; plasma concentrations mirror tissue concentrations.

B- Two-Compartment Model:Most xenobiotics do not instantaneously equilibratewith tissues, but are initiallydistributed to highly perfused organs, and sub-sequently distributed to less perfused peripheral tissues. Example: Digoxin, barbituratesIidocaine.

Metabolism (Biotransformation): Chemical transformation of toxicants, Toxicants can be metabolized from active to inactiveand vice versa,metabolic conversion can be categorized into two stepsor phases, classically known as phase I and phase II.

Phase I metabolism:-

Phase Imetabolism converts apolar, lipophilic xenobiotics into morepolar and more hydrophilic metabolites via introduction orliberation of functional groups that can be used during phaseII.Ituses a wide assortment of reactionsthat processes the xenobiotic via hydrolysis, oxidation, orreduction pathways.

Phase IImetabolism :-

Conjugates either the xenobioticitself or its metabolite formed during phase I metabolismwith a functional group that results in a multifold increase inwater solubility. A xenobiotic may undergo phase I only,phase II only, or both phase I and II, depending on thexenobiotic.

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Factors which affect Biotransformation:

1. ***Enzyme induction:***some chemicals ortoxicantstend to increase amount of metabolic enzymes which lead toincrease biotransformation rate (Phenobarbitone, Glucocorticoids and Alcohol).
2. ***Enzyme inhibition:***Other chemicals ortoxicantstend to decrease amount of metabolic enzymes which lead to decrease biotransformation rate (chloramphenicol and carbon tetrachloride.).
3. ***Age:***In young animals slow metabolism due to slow metabolic enzymes in the liver, also in the old animals.
4. ***Liver diseases:***Also slowing the metabolism, e.g. Liver cirrhosis, parasitic infestation of liver.
5. ***Species variation:***Equine have high rate of oxidation, also glucournidation, Ruminants have high acetylation, Cats, Geese and Fish have low Glucournidation, dog has low acetylation.

Elimination:Removal ofthe toxicantfrom the body

*** Routes of elimination include:**

- **Urine** : mosttoxicants are eliminated through this route.
- **Stool** : (e.g. corticosteroids from biliary system) .
- **lungs**:(e.g. general anesthetics eliminated by expiration) .
- **skin and mucous membranes**: (e.g. rifampin in tears) .

Amount of excreted drug = Amount of filtered drug + amount of active secreted drug – amount of absorbed drug.

Clearance of drug: volume of blood which cleared fromthe toxicantper unit of time

CL= rate of elimination /*C*

Half-life (*t½*):time it takes for the plasma concentration or the amount ofthe toxicantin the body to be reduced by 50%.

$$t_{½} = \frac{0.69}{Kel}$$

0.693: inverse natural log. of 2.

Ke (1/minute):constant of drug elimination, In case ofa toxicantfollowsthe first order of excretion

First-Order Excretion: The rate of excretion of atoxicantis directly proportional to its concentration.

Zero-Order Excretion:The rate of excretion of atoxicantis independent of its concentration

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Metal Poisoning

General Consideration

Metals are unique class of toxicants because of :-

1. They occur and persist in nature .
2. Most of them have some value to human because of their uses in industry, agriculture or medicine.
3. Some of them are essential elements requires in various biochemical , physiological function.
4. They may pose health hazards to the public because of their persist in food , water and air.
5. They have wide range of toxicity , some such as mercury and lead are very toxic while some such as titanium are non-toxic .

Lead poisoning(pb^{+2})

Lead is a bluish white to gray heavy metal that was probably the first toxic element recognized by human and yet still has great relevance today.

Sources of lead toxicity:

- The main sources of lead are the gasoline, paints, construction materials and many other products.
- Drinking water may be appreciably contaminated by Pb from the use of lead and pipes .
- Additional sources of lead have included lead weights (e.g. for fishing or curtains) small lead trinkets , toys, batteries , lead shot and bullets for weapons, lead arsenate pesticides and many other products.

Exposure to lead

1. Cattle and horses are curious and lick or chew on batteries and peeling paint .
2. Puppies and young dogs chew on painted areas and ingest lead objects .
3. Cats have been poisoned by licking lead-contamination dust from remodeling from their coats and paws .
4. Zoo animals and captive birds consume lead objects or lead-based paints used on cages .

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Toxicokinetics

More than 90% of absorbed lead is bound to red blood cells, with small amounts bound to albumin and even lesser amounts present in the plasma as free lead; the unbound lead is distributed widely throughout various tissues.Distribution of Lead (95% in long bones . 4% in brain , liver, kidneys. 1% in blood. Binds into matrix. Released during osteolysis. Lead can be crosses placenta).

The highest concentrations of lead occur within the bone, teeth, liver, lung, kidney, brain, and spleen. Bone serves as a long term storage depot for lead, and enhanced bone remodeling may result in the release of stored bone, precipitating toxicosis long after the original lead exposure.

Mechanism of Action

Lead has multiple effects on biochemical mechanisms within the body, including binding of cellular and enzymatic sulfhydryl groups, competition with calcium ions, inhibition of membrane-associated enzymes, and alteration of vitamin D metabolism. Lead binds sulfhydryl groups, resulting in inactivation of enzymes involved in heme synthesis, such as δ-aminolevulinic acid dehydratase(ALAD) and ferrochelatase, and causing red blood cellabnormalities.

Inhibition of heme synthesis is also thoughtto be responsible for some of the neurologic effects of leadpoisoning; for example, heme depletion may result ininhibition of cytochromeP-450 .

Toxicity and Risk Factors

Young animals absorb lead far more readily than doadults, with up to 50% of ingested lead being absorbed inthe young.Lead absorption can also be enhanced incalcium-, zinc-, iron-, or vitamin D–deficient animals.Conversely,zinc or calcium supplementation may decrease the absorption of lead from the gastrointestinal tract.Lead mayinterfere with the absorption of selenium from the gastrointestinaltractinruminants,resultinginseleniumdeficiency. Co-ingestion of lead and cadmium may increase the severityof clinical signs of lead poisoning.

Cattle are most commonly exposed to lead through ingestion of discarded automotive batteries, farm machinery grease or oil, roofing felt or lead-based agricultural paints, and caulks or putties. Horses and sheep are most commonly exposed by grazing on pastures contaminated by airborne emissions from nearby smelters. Other potential sources of lead exposure for livestock include water from lead-lined pipes, leaded drinking or feeding utensils, and lead arsenatepesticides.

Clinical signs:

Clinical signs of lead toxicosis vary with the species involved, duration of exposure and amount of lead absorbed, and we can summarize them in:

a. **Gastrointestinal signs:** Abdominal pain and diarrhea can be common clinical signs in animal exposed to excess lead. Anorexia is common as well as vomiting in those species that are able.

b. **Neurological signs:** They including depression, weakness and ataxia can progress to more severe clinical signs of muscle tremors or fasciculations, head pressing (especially in ruminants), blindness, seizure-like activity and death.

c. **Hematological signs:** Anemia and stippling of erythrocytes.

Treatment:

In addition to the general treatment steps that listed previously, the antidote of choice in case of lead poisoning are the chelator agents likecalcium disodium*Ethylene-Diamine-Tetra-Aceti*cacid (Ca EDTA),Dimercaprol or*British anti-lewisite*(BAL) andSuccimer (*meso-2, 3-dimercaptosuccinic*or DMSA).

Arsenic poisoning(As)

Arsenic is a yellow to grayish black metalloid , The commercial forms of arsenic are inorganic and organic herbicide and insecticide . Arsenic trioxide is used as a source of other arsenicals . The pentavalent arsenate (H_3AsO_5) and trivalent arsenite (H_3AsO_3) forms inorganic salts of arsenic are used as insecticides and herbicides . The organic forms of arsenic have been used as feed additives for food animal .

Sources of Arsenic toxicity:

1. Area around mining or smelting sites .
2. In properly discarded or stored of pesticides such as lead arsenate and arsenic trioxide .
3. Burning of wood products treated with arsenic compound .
4. Some ant baits contain sodium or potassium arsenate which can be consumed by small animals .
5. Arsine (AsH_3) is an industrial gas of charging storage batteries .
6. Therapeutic use of Thiacetasamide in some dogs .

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Mechanism of Toxicity

The soluble arsenicals are readily absorbed from gastrointestinal tract and through the skin .

1. Trivalent arsenicals inhibit cellular respiration , they bind to sulfhydryl compound especially lipo-acid (a tissue respiratory enzyme cofactor) and α- keto-oxidases .
2. Pentavelant inorganic arsenicals appear to substitute for phosphate in oxidative phosphorylation .the uncoupling oxidative phosphorylation produces a cellular energy deficit.
3. Hydride gas of arsenic combines with hemoglobin and be oxidized to hemolytic metabolite .

Clinical Signs:

Arsenic is available in two forms: Inorganic and Organic each form of them has two valence: Arsenic trivalent and Arsenic pentavalent and the severity of their toxicity are illustrated in this scheme:***(Inorganic As^{+3}>Inorganic As^{+5}>Organic As^{+3}>Organic As^{+5})***

- **Clinical signs of Trivalent arsenate poisoning:**

Abdominal pain or colic, vomiting, a staggering gait and weakness, clear incoordination, rapid weak pulse and shock, diarrhea, followed collapse, and death. In case of high exposure death will occur directly within few minutes to hours.

- **Clinical signs of Pentavalent arsenate poisoning:**

Poisoning occurs within 3 days of a high dose or after chronic exposure. Most noticeable are the neurological signs. The animal is generally bright and alert but uncoordinated. The animal may or may not be blind, and these animals may have erythema in the skin. Some of the neurological damage may be reversible unless the nerves are damaged.

Treatment:

1. General :- Emergency and Supportive care include correction of shock , acidosis and dehydration . Emetic and gastric lavage may be used if ingestion is recent .
2. Specific :-
    a) Dimercaprol(BAL) it is relatively in effective unless given before the onset of clinical signs .
    b) Thioctic acid is more effective for arsenic poisoning in cattle .
    c) Succimer is a water soluble analogue of dimercaprol and is preferred chelator and available .

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Mercury poisoning(Hg)

Forms :- Mercury exists in liquid form . It is also present in the environment as inorganic and organic compounds .

Organic Hg —Oxidation→ Inorganic

Sources of Mercury toxicity:

1. Mining and smelting of producing metals from their sulfide ores .
2. Burning of fossil fuel .
3. Production of steel , cement , phosphate , paper-pulp industry and electrical equipment manufacture .
4. It is commonly used in thermometers, barometers, blood pressure devices, batteries, electric switches .
5. Some of mercury compounds are used as fungicides, while others are used for medicinal purposes, e.g. laxatives, deworming agents, antiseptics, and disinfectants.

Mechanism of Toxicity

The mercuric ion binds covalently with sulfur and inhibit sulfhydryl containing enzymes , mercuric salts may also bind to protein . organic alkyl mercurial interfere with metabolic activity and prevent synthesis of essential proteins leading to cell degeneration and necrosis .

Toxicity

It is occur due to consuming grain treated with mercury fungicide or fish contaminated with methyl mercury . Mercury toxicity is dose related .

1. Acute toxicity occurs due to ingestion large amount of inorganic mercury , death occurs through several hours .
2. Chronic toxicity occurs due to ingestion small amounts of inorganic mercury for long period .

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Clinical signs:

In Cattle: include ataxia, neuromuscular incoordination, and renal failure, followed by convulsions and a moribund state. Average time from ingestion to death is reported to be about 20 days.

In Horses : signs of acute toxicity include severe gastroenteritis and nephritis. In chronic cases, signs may include neurological dysfunction, laminitis, in addition to renal disease which is characterized by glycosuria, proteinuria, phosphaturia, reduced urine osmolarity, reduced glomerular filtration rate, azotemia, and elevated creatinine and blood urea nitrogen.

In Sheep : the poisoning is characterized by severe neurological symptoms, and tetraplegia.

Treatment:

1. Protein (egg and milk) must be given orally in acute cases .
2. Oral sodium thiosulfate (0.5 – 1) g / Kg.Bw bind mercury .
3. Stomach washing by sodium formaldehyde sulfa oxalate sodium thiosulfate to reduce of divalent mercury (Hg^{+2}) to monovalent (Hg^{+}) .
4. Dimercaprol(BAL) specifically for inorganic mercury (3 mg / kg.BW) intramuscular for three days .

Cadmium poisoning(Cd)

Cadmium is a soft,malleable , ductile , toxic, bluish-white bivalent metal . It is similar in many respects zinc tobut forms morecompounds.

Sources of Cadmium toxicity:

Numerous compounds are formed from cadmium and thus it is used in batteries, solders, semiconductors, solar cells, plastics stabilizers, and to plate iron and steel. All soil and rocks contain some cadmium. It can enter the environment from zinc smelting and refining, coal combustion, mine wastes, iron and steel production and from the use of rock phosphate and sewage sludge as fertilizers.

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Mechanism of action

Once inside the cell , free cadmium binds to protein sulfhydral groups , disrupt the cellular redox cycle , depleting glutathione , and eliciting intracellular oxidant damage . cadmium ions can displace zinc and other divalent metals from their binding sites on metalloproteinase , for example in the testis , cadmium can interfere with zinc – proteins , leading to wide spread apoptosis and necrosis .

Toxicity

1. Acute effects of cadmium exposure result mainly from local irritation .
2. Chronic exposure , in this form of toxicity , kidney lesions is predominant . The primary site of action is the proximal tubule , the tubular damage results in their inability to reabsorb small molecular proteins , the major one of which is $\beta 2$ – macroglobulin .

Clinical signs:

1. The clinical manifestation of acute effects include nausea , vomiting and abdominal pain .
2. Aminoaciduriaand glycosuria .
3. Hypercalciuria , which probably in conjunction with altered bone metabolism may lead to osteomalacia .
4. Effect on the respiratory system result from inhalation exposure include chronic bronchitis , progressive fibrosis of lower airway an emphysema
5. Hypertension ,which may be result from sodium retention , vasoconstriction , and hyperreninemia .
6. Carcinoma has been reported among occupational workers .
7. Itai – Itai disease characterized by bone deformity .

Treatment:

In animals , cadmium toxicosis is prevented by minimizing exposure in the environment and in feedstuffs . There is no effective treatment for cadmium toxicity .Treatment will be designed to help manage and relieve symptoms , can be given **vitamin D** for the weak bones .

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Thallium poisoning(TL)

It is a highly toxic soft gray malleable poor metal resembles. Tin but discolored when exposed to air.

Sources of Thallium toxicity:

Approximately 60-70% of thallium is used in the electronics industry , and the rest is used in thepharmaceutical industry and in glass manufacturing . It is also used in infrared detectors. Because of its high toxicity it used as pesticide andinsecticide , but its uses has been reduced or banned in many countries.

Clinical signs:

The diagnosis of thallium poisoning may be difficult, because it is often unsuspected. The cardinal features are gastroenteritis, peripheral neuropathy due to CNS necrosis, and then later, alopecia.

Treatment:

By following the general steps of treatment and administration of chelator agents likecalcium disodium*Ethylene-Diamine-Tetra-Acetic*acid (Ca EDTA),Dimercaprol or*British anti-lewisite*(BAL), Dithiazone and Prussian blue.

Sulfur Poisoning(S)

It is an abundantmultivalent non-metal element. Sulfur, in its native form, is a yellowcrystalline solid. In nature, it can be found as the pure element and as sulfide and sulfateminerals. It is an essential element for life and is found in two amino acids , cysteine and methionine .

Sources of Sulfur toxicity:

Sulfur is presented in sulfuric acid, fertilizers, pigments, dyes, drugs, explosives, rubber, insecticides, and detergents, as well as many inorganic salts and esters. Although uniformly found in nature, industrialized countries are the largest users of sulfur materials.

Clinical signs:

The clinical signs of sulfur toxicity are depend on the term, route of exposure and the species of animal. The main clinical manifestations are:Abdominal pain, colic, rumen stasis, fetid diarrhea, dehydration, metabolic acidosis, tachypnea, recumbency, and hydrogen sulfide smell are expected clinical signs. Irritation, edema, and hemorrhage of the gastrointestinal tract and respiratory tract should be expected. In addition, renal tubular necrosis can be seen.

Treatment:

By following the general steps of treatment and administration of**Nitrite**in cases of acute and sub-acute poisoning with sulfur to get rid from harmful effect of hydrogen sulfide by induction of methemoglobinemia with nitrite to allow for the formation of sulfmethemoglobin as same mechanism of cyanide poisoning treatment.

Phosphorus poisoning(P)

Anmultivalent and non-metal element found in inorganic phosphate rocks. Due to its high reactivity, phosphorus is never found as a free element in nature on Earth. Phosphorus is a component ofDNA , RNA, ATP and also the phospholipids which form all cell membranes. It is thus an essential element for all living cells .

Sources of Phosphorus toxicity:

The most important commercial use of Phosphorus -based chemicals is the production offertilizers . Phosphorus compounds are also widely used inexplosives , nerve agents, friction matches , fireworks , rodenticides , toothpaste and detergents .

Clinical signs:

Phosphorus, in the form of white or yellow phosphorous, has historically been used as a rodenticide but is uncommon today. Initial clinical signs following ingestion would include gastroenteritis with vomiting and diarrhea. If the animal survived several days it would often develop a secondary phase of severe liver damage with renal insult also occurring.

Treatment:

Till this time there are no determined or suggested antidote for phosphorus poisoning, but the administration of calcium to correct the normal ratio of Ca : P (2:1) in the body is may be possible in addition to follow the general steps of toxicity treatment.

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Copper (Cu)

There are numerous sources of copper available in the animals environment .

1. Molybdenum and sulfate bind with copper to form insoluble copper sulfide , So the deficiency of molybdenum in diet can result excessive copper absorption and increased hepatocellular copper storage .
2. The feeding of calf and horse ration (high level of copper) to sheep .
3. The feeding of monensin in high copper ration to young animals can increase intestinal absorption of copper .
4. Certain fungicides and algaecides .
5. Footbaths contain (CuSo4) due to drainage in waste collection ponds .

Forms

1. Chronic copper toxicity is usually chronic problem in sheep , because of slow buildup of copper in liver followed by quick release from hepatocyte .
2. Acute toxicity due to the ingestion of large amount of copper sulfate or ingestion of excessive copper compounds .

Mechanism of toxicity

Copper exerts its toxic action primarily on the liver , because there are excessive accumulation of copper in hepatic lysosomes . the excessive copper causes damage to the cell membrane and death of hepatocyte . the large amounts of free copper are released into circulation , the copper damages the membranes of red blood cells , causing release of hemoglobin .

Toxicity and risk factors

Sheep are sensitive to copper , whereas cattle , horses , swine , chicken , turkeys and dogs are relatively resistant . Thirty parts per million of copper in diet of sheep can be toxic , whereas cattle can handle up to (50 ppm) in the ration .

Sheep are rarely show clinical signs until the animal is stressed . Which are hemoglobinurea ,icterus , anoxia and death .while the lesions are dark red or blush black kidney (gun metal blue kidney) , swollen friable liver . In acute toxicity hemorrhages and edema of abomasum or stomach mucosa . The intestinal contents and feces may have a faint blue-green color .

Veterinary Toxicology

Treatment and control

The treatment of acute copper toxicity is often unsuccessful

1. The copper / molybdenum ratio 6/1 to 10/1 in the diet is greatly assist in decrease the chronic toxicity .
2. Sulfur level greater than 0.35% assists in lowering copper toxicity .
3. The zinc addition to the diet can decrease copper absorption .
4. Pasturing animals on old orchards where copper – containing pesticide have been used should be avoided .
5. Ammonium molybdate(50 – 500) mg PO and sodium thiosulfate (300-1000) mg PO for three weeks .
6. D-pencillamine(10 – 15) mg / kg. BW. PO bid chalets copper and promote urinary excretion .

Molybdenum (Mo)

Molybdenum in its natural from doesn't exist in the elemental state , it is found in copper , lead and tungsten (wolfram) ores . The predominant from of molybdenum in soil and water is molybdateanion . The sources of molybdenum are :-

1. Combustion of fossil fuels .
2. Mineralization of lakes .
3. Emission from aluminum smelting , steel alloy factories .

Forms :-Ruminants are the most susceptible species

1. Sub-acute :- Continues grazing of forage contaminated with molybdenum , caused illness and death in cattle within approximately two weeks .
2. Exposure to (6.2 ppm) of molybdenum in forage for (5 -12) months caused epiphyseal dystrophy in calves .

Mechanism of toxicity

Molybdenum is required for metallo enzymes including xanthine oxidase , xanthine dehydrogenase , aldehyde oxidase and sulfide oxidase . molybdenum in the blood binds with α– macroglobulin (is a plasma protein enzyme inhibit protease enzymes) in the membrane of erythrocytes , where it is enhance the resistance of the membrane to rupture . The increasing delivery of molybdenum and sulfur increases the amount of trichloroacetic acid insoluble – Mo – Cu protein complex found in plasma .Trichloroacetic acid solubility is measure of available copper in plasma . However clinical signs of copper deficiency can be observed .

Signs and Lesions

Molybdenum (teart) is a form of molybdenum toxicity that produces a disease in ruminants similar to copper deficiency . the clinical signs include loss of body weight , anemia , diarrhea , decrease milk production , alopecia , central nervous signs (sway back in lambs) and achromotrichia . the gross lesions are include swollen and friable liver and swollen pale kidneys .

Diagnosis

Molybdenum diagnosis depend on clinical signs and the concentration of molybdenum in the blood , liver and kidney . the most common finding with molybdenum intoxication is the high concentration of molybdenum in liver and low concentration of copper .

Treatment

1. Copper should be added to the diet to give 4:1 to 10:1 copper to molybdenum ratio .
2. The sulfa to molybdenum ratio should be less than 100:1 .
3. Copper glycinate injection to cattle .
4. Copper sulfate can be added directly in the water for cattle .

Zinc(Zn)

It is an essential element in mammals and birds and is a component of approximately 200 metaloenzymes .also zinc has an essential role in nutrition and consequences of nutritional deficiency.

Uses

Zinc is an economical metal to use and is relatively nontoxic , table below details some of those uses .

Uses	purposes
Zinc oxide	**Paint ,sun protectants ,rubber activator , diaper rush ointment.**
Zinc chloride	**Wood preservative and deodorant.**
Zinc methyl Zn $(CH_3)_2$	**Number of organic synthesis.**
Zinc stearate	**A lubricative plastic additive.**

Veterinary Toxicology

Toxicity

The different forms of zinc have different form of toxicities .the zinc salts have median lethal dose (**LD_{50}**) of approximately 100mg/kg.BW.zinc oxides are less toxic ,and frequently found in ointments.

1- Acutetoxicities.
2- Asub-acute zinc toxicities:-it is due to the ingestion of pennies ,which are 96% zinc by dogs.
3- Chronictoxicities in foals have non-painful joint enlargement lasting 7-21 days.

The clinical findings include :-

1. Hypercreatinemia.
2. Azotemia.
3. Hyperphosphatemia.
4. Glanular casts in the urine.
5. Non-viable new borns.
6. Lethargy ,anorexia followed by diarrhea.
7. Decrease milk production.
8. Anemia and icterus.
9. Diagnostically ,there may be a radio dense area in the gastrointestinal tract indicating the presence of zinc or some metal such as lead.

Treatment

1. Removal of the source the toxin from the animal ,will allow the normal excretory pathways to work appropriately.
2. Supportive therapy are critical to the patient s recovery.

Veterinary Toxicology

Insecticides

Insecticides play a most relevant role in the control of insect pests, particularly in developing countries. All of the chemical insecticides in use today are neurotoxicants, and act by poisoning the nervous systems of the target organisms .The central nervous system of insects is highly developed and not unlike that of mammals, and the peripheral nervous system, though less complex, also presents striking similarities . Thus, insecticides are mostly not species-selective with regard to targets of toxicity, and mammals, including humans, animals are highly sensitive to their toxicity.

Organic Phosphorus Compounds (OPC)and Carbamates (CMs)

Organophosphates (OPC) and carbamates (CMs) are commonlyused as pesticides in agriculture, industry, andaround the home/garden throughout the world. In addition,these chemicals are used as parasiticides in veterinarymedicine. Both types of chemicals produce theirtoxicity by virtue of inhibition of acetylcholinesterase(AChE) enzyme, which terminates the action of the neurotransmitteracetylcholine (ACh) at the synapses in nervoustissue and at the neuromuscular junctions. Thesechemicals are referred to as "Anticholinesterases". Someof the OPCwith strong AChE inhibiting potential are alsoused as nerve agents or nerve gases.

Clinical signsof toxicity:

Most animal poisoning cases in the field are acute innature. Onset of clinical signs usually occurs within15 min to 1 h, which is soon followed by the signs of maximalseverity, although these timings tend to vary dependingupon the compound and its dose and species.

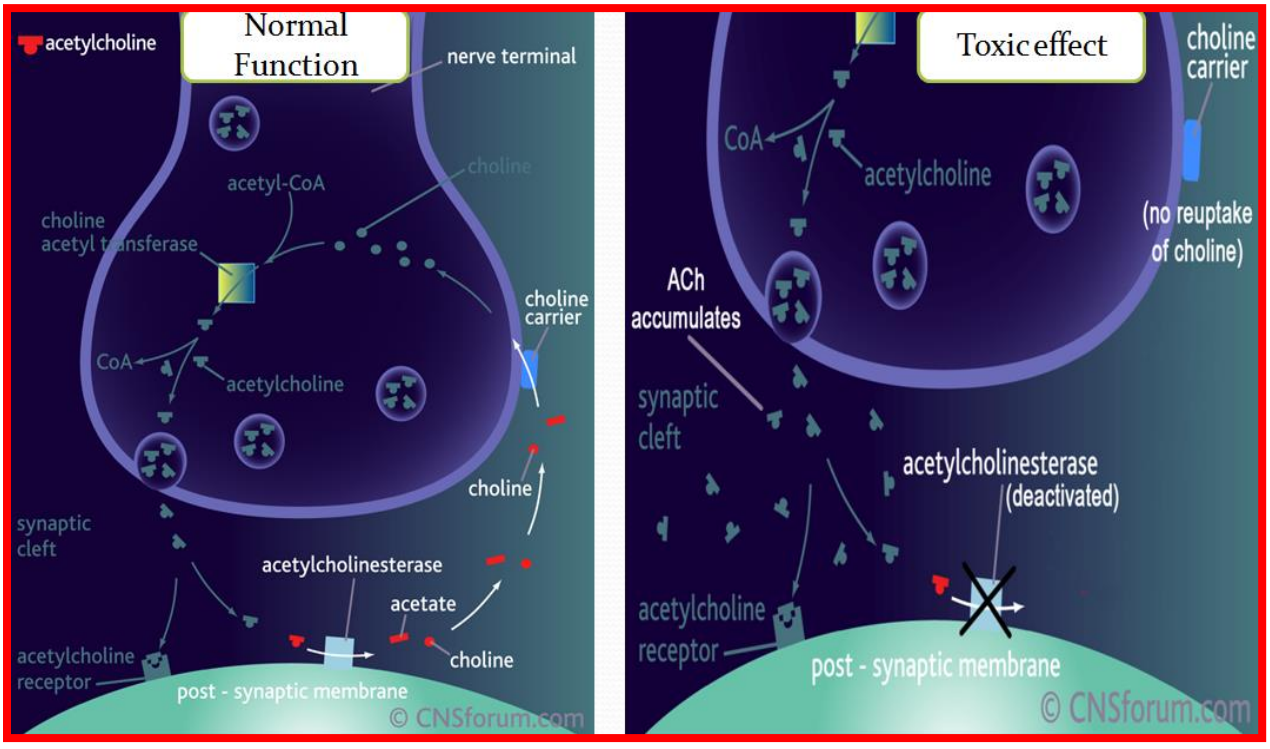
The clinical signs can be classified as:-

1. **Muscarinic:**Muscarinic receptor-associatedeffects are manifested by vomiting, abdominal and chestpain, salivation, lacrimation, urination, diarrhea (SLUD),miosis (pinpoint pupils), tracheobronchial secretion, lungedema, and cyanosis.

2. **Nicotinic:**The nicotinic receptor-associatedeffects are produced on autonomic ganglia and skeletalmuscles, and the affected animals show twitching of muscles,tremors, followed by convulsions, and seizures. Thiscondition may lead to paralysis.
3. **Central:**Central effects include apprehension, stimulation, followed by depression. Theaffected animals mayalso show restlessness, ataxia,stiffnessof the neck, and coma. Death occurs due to respiratoryfailure and cardiac arrest.

Treatment:

1. **Organic Phosphorus Compounds:**In the case of OP poisoning, antidotal treatment requiresthe combined use of**Atropine sulfate**and**pyridine-2-aldoxime methochloride*(2-PAM).***Atropine will block the effect of acetylcholine while **2-PAM** will reactivate the Acetylcholinestrease(AchE)enzyme.
2. **Carbamates:**administration of**Atropine**only because that the2-PAM and other oximes areineffective in carbamates poisoningcases.



Veterinary Toxicology

Pyrethrins and pyrethroids

- Pyrethrins are the insecticidal compounds obtained fromthe flowers of the plant*Tanacetumcinerariaefolium*, alsocalled*Chrysanthemum cinerariaefolium*or*Pyrethrum cinerariaefolium*.WhilePyrethroids are syntheticanalogs of pyrethrins.
- Pyrethrins cause hyperexcitability with very little cytotoxicity.The molecular targets of the pyrethrins andpyrethroids are similar in mammals and insects and includevoltage sodium, chloride, and calciumionchannels,gamma-aminobutyric acid (GABA)-gated chloride channels,nicotinic receptors, membrane depolarization andintercellular gap junctions.
- Mammals are less susceptible topyrethrin and pyrethroidtoxicoses than insects primarilybecause they have a faster metabolic clearance higher bodytemperatures and a lower affinity for the pyrethrins/pyrethroids.

Clinical signsof toxicity:

Clinical signs that result from the toxicity with these compounds can beconfused with poisoning by other pesticides, such as organophosphates.

Clinical signs include salivation, vomiting, hyperexcitability, tremors, seizures, dyspnea, weakness, prostration and death.

Treatment:

There is no specific antidote for pyrethroid toxicity, animals should be treated symptomatically.In addition to the general steps of toxicity treatment,Supportive therapybyusing**Diazepam**or**Barbiturates**to control hyperexcitability or seizures can be used.**Atropine**can beused to control excess salivation or gastrointestinalhyper motility.

Organochlorines

Chlorinated compounds, cyclodienes such as aldrin and dieldrin,Dichlorodiphenyltrichloroethane***(DDT),***Kepone, ChlordeconeandChlordaneused as insecticides, became available for use in the 1940's.

Organochlorins are exert their toxicity through two mechanisms:-

- Some Organochlorines alter the action potential of the neuron.
- Another group of these chemicals act by inhibiting GABA association with its postsynaptic receptors.

Clinical signsof toxicity:

Acute Toxicity: Initially nausea and vomiting; thenweakness, paresthesias, tremor, clonus, seizures,fever; seizure activity, respiratory paralysis,respiratory arrest and death.

Chronic Toxicity: Chlordane causes leukemia andthrombotic thrombocytopenic purpura (TTP);Chlordecone causes pseudotumorcerebri andmale infertility.

Treatment:

In addition to the general step of poisoning treatment and for control the seizures we can use **DextroseandThiamineorBenzodiazepinesorPhenobarbital.**

Veterinary Toxicology

Herbicides

Chemical used to kill or remove herbs that interfere with agricultural production .The risk to animal may arise fromconsuming thetreated forages orwater,also they might cause increase inconcentration ofcyanide and nitrate in plantespeciallyyounger one.

Paraquat and Diquat

Sources. Paraquat is one of the most efficient herbicides and often the herbicide of choice to control flourishing vegetation. However, it is one of the most specific pulmonary toxicants known, and a high mortality rate is encountered in poisoning cases.

- Water-soluble, dark brown liquid, looks like Coca-Cola®; rapidgastrointestinalabsorption, little skin and lung absorption; common suicide agent in IndiaandSoutheastAsia.
- Very corrosive to gastrointestinaltract,causedamage to pulmonaryandrenal tubular lining cells; increased pulmonary O_2toxicity(Hyperoxia).

Mechanism of action

Paraquat can form free radicals, and tissue necrosis is associated with the same mechanisms of superoxide-induced peroxidation as observed with diquat. In addition, it has special affinity for and concentrates in the lung as a result of a diamine-polyamine concentrator system in alveolar epithelial cells.Paraquat is excreted through the kidney.

Clinical signs:

Paraquat is an irritant and a vesicant and thus can cause considerable local toxicosis (erythema,blistering, irritation, blistering of skin, and corneal irritation) from topical exposure, such as splashing at time of application. In uncomplicated cases, full recovery is possible. In acute poisoning from ingestion, the disease typically occurs in three phases.

- The initial phase reflects the caustic action of paraquat with the development of pain in the gastrointestinal tract. Pain is followed by vomiting and aphagia.

- The second phase, renal failure accompanied by hepatocellular necrosis, develops by the second or third day. The renal tubulopathy often resolves uneventfully by the time of death.
- The third phase is delayed development of pulmonary fibrosis and is responsible for the poor and usually fatal prognosis.

In sub-acute or chronic poisoning low doses of paraquat allow hyperplasia of type II alveolar epithelial cells and healing by fibrosis. In such cases, cyanosis develops rapidly when the animal is exercised, reflecting the increasing mismatch of ventilation with perfusion, the increasing alveolar-arterial oxygen gradient, and desaturation of hemoglobin with oxygen.

Treatment:

- No antidote.
- Administer immediate adsorbentlike activated charcoal.
- Noemesis or lavage secondary due toincreasedgastrointestinalperforation risks.
- **Use**cathartics likesorbitol.

N.B.\ Diquat: same as paraquat, but not taken up by alveolar lining cells, consequently less lung injury, oxygen toxicity, and residualfibrosis.

Cyanogenic plants and Cyanide Poisoning

- Cyanide, hydrocyanic acid, hydrogen cyanide (HCN) and prussic acid are all terms relating to the same toxic principle. Cyanide is used as a fumigant and in chemical synthesis; Cyanide salts are used in metal cleaning, hardening, refining and in the recovery of gold from ores. Burning nitrogen-based polymers used in plastics, fabrics and seat covers releases HCN.
- Seeds of members of the*Rosaceae*family including apple, cherry, peach and apricot do contain cyanogenic glycosides.
- All animal species are susceptible to cyanide poisoning. The ability of rumen microbial flora to rapidly hydrolyze cyanogenic glycosides makes ruminants particularly at risk of cyanide intoxication from plant sources.

- Cyanide ion combines with ferric (trivalent) iron in the cytochrome oxidase system, blocking electron transport and molecular oxygen transfer from oxyhemoglobin to tissues, causing reversible cellular hypoxia or histotoxic anoxia.

Toxic principle

Hydrogen cyanide (HCN) is formed when the glycosides are hydrolyzed by enzymes in plants or by rumen micro-organism .

β-glycosidase
Cyanogenic glycosides Sugar + aglycone

AglyconeHCN + aldehyde or Ketone

The glycosides occur in vacuoles in plant tissue while the enzymes are found in the cytosol . Damage to the plant form wilting , trampling , mastication , frost , results in the enzymes and glycosides coming together causing hydrogen cyanide to be formed . **β**-glycosidase are also produced by rumen microorganism , for that ruminants are more sensitive to cyanogens than non-ruminants .

Clinical signs of toxicity:

Onset of clinical signs is peracute (especially in ruminants) and includes apprehension, pronounced polypnea then dyspnea. The pupils dilate and mucous membranes may be pink and venous blood a bright cherry red. Weakness, voiding of urine, collapse, paddling and death follow within a few minutes.Sub lethalcases may recover within the hour.

Treatment:

The antidote of choice in humans, dogs and probably most other animals is**Sodium nitrate**in combination with**Sodium thiosulfate**. Ruminants can be treated with**Sodium thiosulfate**alone.

Veterinary Toxicology

Nitrites and Nitrates

- Nitrate and nitrite are compounds that contain a nitrogen atom joined to oxygen atoms, with nitrate containing three oxygen atoms and nitrite containing two. In nature, nitrates are readily converted to nitrites and vice versa.
- Nitrates are used primarily to make fertilizer, but they are also used to make glass and explosives. These compounds also are used in various chemical production and separation processes. Nitrites are manufactured mainly for use as a food preservative, and both nitrates and nitrites are used extensively to enhance the color and extend the shelf life of processed meats.
- Nitrates are naturally present in soil, water, and food. In the natural nitrogen cycle, bacteria convert nitrogen to nitrate, which is taken up by plants and incorporated into tissues. Animals that eat plants use the nitrate to produce proteins. Nitrate is returned to the environment in animal feces, as well as through microbial degradation of plants and animals after they die.
- Microorganisms can convert nitrate or the ammonium ion (which is a nitrogen atom combined with four hydrogen atoms) to nitrite; this reaction occurs in the environment as well as within the digestive tract of humans and other animals especially in ruminants.
- The nitrite anion causes vasodilatation and oxidizes ferrous iron in hemoglobin to the ferric (trivalent) state forming methemoglobin which cannot accept molecular oxygen. As the percentage of methemoglobinemia rises oxygen starvation to tissues increases and blood becomes chocolate brown in color.

Clinical signs of toxicity:

Clinical signs of nitrate-nitrite toxicosis in animals (especially in ruminants) include weakness, cyanosis of mucous membranes, ataxia, collapse and death. Increased respiratory rate may be noted in some animals. Affected animals may remain standing then collapse and die within minutes.

Dead animals may be found in sternalrecumbencyor lying on their side. Blood is dark and may have an obvious brown color when drawn into a syringe or spread on a white cloth .

Treatment:

Treatment is with intravenous administration of**Methylene blue**, other dyes such as**Tolonium chloride**(tolonium blue) are effective in reducing methemoglobin to hemoglobin but have a narrow therapeutic index.

Tropane Alkaloids Producing plants

The family Solanaceae contains several genera that are toxicdue to the tropane alkaloids atropine and scopolamine.

-***Atropa*(belladonna).**

-***Hyoscymus*(henbane) .**

-***Brugmansia*(angel's trumpet) .**

-***Datura*(jimsonweed) .**

They can all causeincidentalspoisoning but onlythe genus*Datura*appears to be of veterinary significance.

Mechanism of action

All the produced alkaloids are muscarinic receptor antagonists compete with acetylcholine(Ach) for a common binding site on the muscarinic receptorsand thus block the action of ACh at muscarinic neuroeffectorsites on smooth and cardiac muscle, gland cells,in peripheral ganglia and in the central nervous system(CNS). In general they cause little blockade at nicotinicreceptor sites.

Clinical Signs

CNS depression manifested as drowsiness, amnesia and fatigue. The acute toxic effects commonly seen with atropine are mydriasis and cycloplegia, dry mucous membranes and tachycardia. At higher doses central nervous excitation becomes more prominent resulting in restlessness, irritability, disorientation, hallucination and delirium. At still larger doses, stimulation is followed by depression leading to circulatory and respiratory failure after a period of paralysis and coma.

In the horse, additionally, the motility of the large intestineis seriously affected and either an acute paralytic ileusresults with consequent death from acute complicationslike torsion, strangulation or tympany, or in more chroniccases recalcitrant impaction colic develops.

Treatment

Treatment is limited to controlling the signsof the animal. Mania can be controlled only with tranquilizers(diazepam or phenobarbital) or anesthesia (pentobarbital).Occasionally large doses of parasympathetic drugsmay be of use.(ReversibleAchE can be used like Physostigmine, Neostigmine)However, arecoline and pilocarpine are notrecommended because they tend to depress breathing.

Veterinary Toxicology

Mycotoxins

A **mycotoxin** :-From Greek (mykes, mukos) "fungus" and (toxikon) "poison") is a toxic secondary metabolite produced by organisms of the fungi kingdom, commonly known as molds. The term 'mycotoxin' is usually reserved for the toxic chemical products produced by fungi that readily colonize crops. One mold species may produce many different mycotoxins, and the same mycotoxin may be produced by1 several species.

Most fungi are aerobic (use oxygen) and are found almost everywhere in extremely small quantities due to the minute size of their spores. They consume organic matter wherever humidity and temperature are sufficient. Where conditions are right, fungi proliferate into colonies and mycotoxin levels become high. The reason for the production of mycotoxins is not yet known; they are necessary for neither growth nor the development of the fungi. Because mycotoxins weaken the receiving host, the fungus may use them as a strategy to better the environment for further fungal proliferation.

Aflatoxins

Source of toxicity:

Aflatoxins are a type of mycotoxin produced by *Aspergillus* species of fungi, such as *A. flavus* and *A. parasiticus*. The umbrella term aflatoxin refers to four different types of mycotoxins produced, which are B_1, B_2, G_1, and G_2.Aflatoxin B_1, the most toxic, is a potent carcinogen and has been directly correlated to adverse health effects, such as liver cancer, in many animal species.

Aflatoxins are largely associated with commodities produced in the tropics and subtropics, such as corn, peanuts, cottonseed, rice, sweet potatoes, potatoes, wheat, oats, barley, millet, sesame, sorghum, cacao beans, and almonds and other nuts. Other less common sources include soybeans, copra and coconut, safflower, sunflower, palm kernels, cassava, and spices (cayenne pepper, chili powder, dried chili peppers, black pepper, capsicum peppers,and nutmeg).

Mechanism of action

The reactive metabolites, particularly the epoxide, bind with cellular components including nucleic acids, subcellular organelles, and regulatory proteins that disrupt normal anabolic and catabolic processes. The results include disruption of organ function,carcinogenesis, immunosuppression, mutagenesis, and teratogenesis.

The main effects of aflatoxin are related to liver damage. If the dose is sufficient to produce an acute toxicity, it results in an increased clotting time and hemorrhage, especially in the intestinal lumen. There is also edema of the gall bladder. Acute poisoning causes hepatitis and necrosis of liver cells, resulting in prolonged blood clotting time, with affected animals dying fromsevere hemorrhages.

In subacute cases of poisoning, the liver lesions are those of regeneration and repair ratherthan cell necrosis. The bile duct cells proliferate and scar tissue forms. The rate of protein formation and the growth rate are depressed but the animal may not die. In chronic cases, the lesions are those of chronic liver dysfunction. These usually include icterus, fibrosis or cirrhosis of the liver, ascites and pulmonary edema.

Clinical signs: The aflatoxin dose and duration of exposure determine the time of onset and observed effects.

- **Acute Aflatoxicosis:** anorexia, depression, weakness to prostration, dyspnea, emesis, diarrhea often with blood and mucus, fever followed by subnormal temperature, convulsions (dogs), and epistaxis may be seen.
- **Chronic Aflatoxicosis:** Concurrent with the degree of hepatic damage, the disease might advance to anemia, jaundice, anorexia, and depression. Dogs more often develop gastrointestinal disturbances with occasional hemorrhage and ascites. Poults and ducklings have loss of appetite, appearance of nervous symptoms, and, in young birds, high and rapid mortality. With prolonged feeding ducks are more likely than poultry to develop tumors.

Treatment and control

- No antidote or specific treatment exists for aflatoxicosis beyond prompt removal from the contaminated source. Optimizing the quality of the diet, with particular attention to protein, vitamins, and trace elements, aids in recovery but does little to repair the damage done.
- Procedures to prevent crop damage, such as insect control, can decrease fungal invasion. Handling corn to minimize seed coat damage and drying to 15% or less prevents mold growth and production of additional toxin. Mold retardants, such as propionic acid, can help in storage but do nothing to the toxin that was produced before harvest.

Citrininand Ochratoxin

Source of toxicity:

- Ochratoxins and citrinin are produced by*Aspergillus*and*Penicillium*species. Multiple species of both genera have been found to produce ochratoxin; however,*A. ochraceus*(*A. alutaceus*) and*P. verrucosum*are most commonly associated with disease.
- Ochratoxins, often including citrinin, have caused problems from contaminated corn, barley, rye, and wheat; they are also found in oats, soybeans, buckwheat, rice, sorghum, white beans, peanuts, Brazil nuts, surface of hams, red pepper, black pepper, coffee, decaying vegetation, and soil citrinin can persist in nature for several months.

Mechanism of Action.

Ochratoxin is thought to act by at least three defined mechanisms:

(1)Inhibitionof phenylalanine metabolizing enzymes.

(2)Promotionof lipid peroxidation.

(3)Inhibitionof mitochondrial adenosine triphosphate (ATP) production.

While Citrinin can cause parasympathomimetic activity such as vasodilation bronchoconstriction, and increase in muscular tone.

Clinical Signs:-

Acute poisoning with high doses of OAresults in gastroenteritis, diarrhea, emesis, tenesmus, depression,anorexia, and dehydration. Elevated body temperature,bilateral purulent conjunctivitis, tonsillitis, polydipsia, polyuria,and bloody feces can also occur from high doses.

The mycotoxin concentrations more often found in fieldcases with chronic exposurecause a slower onset and oftensubtle signs related to kidney disease. Water intake andurination frequency is increased. Production parameters (e.g.,weight gain, egg production, feedefficiency) decrease.

Treatment.

1. Agents that slow absorption, such as activatedcharcoal, may be of value in acute poisoning.
2. Supportivetherapy for the kidney disease that results from these toxinsdepends on the degree of organ damage and the particular physiologic abnormalities that warrant intervention.
3. Ascorbic acid added to the diet (at 300 ppm) partiallyameliorates the negative effects of OA intoxication on eggproduction and physiology in laying hens.

Ergot(Ergotism)

Source of toxicity:

Speciesof Claviceps fungi in general or, more specifically, refer to the visible fungal growth (sclerotium or ergot body) formed by*Clavicepspurpurea*on rye (*Secalecereal*).

Mechanisms of Action.

Ergopeptine:Themechanisms of action of the ergopeptine alkaloids involvevasoconstrictionassociated with D_1dopaminergic receptorinhibition and partial agonism ofα1-adrenergic and serotoninreceptors by ergopeptine alkaloids. In addition, stimulationof D_2-dopamine receptors by ergopeptine alkaloidshas been shown to decrease prolactin secretion by lactotropeslocated in the anterior pituitary. Vasoconstriction andhypoprolactinemia are either directly or indirectly associatedwith the pathogenesis of many of the clinical abnormalitiesnoted in ergotism.

lysergic acid amide:The sedative properties of lysergicacid amide may be mediated by a neurotransmitter imbalancein the pituitary and pineal glands involving receptorsfor norepinephrine, epinephrine, dopamine, serotonin, andmelatonin.

Clinical signs:

Traditionally ergotism has been divided into the

1. Gangrenous or cutaneous.
2. Hyperthermic.
3. Reproductive.
4. Nervous forms.

Treatment:

Byremovingofergot-contaminated pastures, hay, grains, orprocessed feedsandfollowing the general steps of treatment.

Veterinary Toxicology

BIOTOXINS (ZOO TOXINS)

Biotoxins

The term "biotoxin" is sometimes used to explicitly confirm the biological origin.Toxins produced by microorganisms are important virulence determinants responsible for microbial pathogenicity and/or evasion of the host immune response.

Biotoxins vary greatly in purpose and mechanism, and can be highly complex (the venommay be contains dozens of small proteins, each targeting a specific nerve channel or receptor), or relatively small protein.

Biotoxins in nature have two primary functions:

Predation (spider, snake, scorpion, jellyfish, wasp) .

Defense (bee, ant, termite, honeybee, wasp, poison dart frog) .

SnakeVenoms

Actions of snake venoms can be said to be broad ranging in severalareas A simplistic approach would group toxincomponents as Neurotoxins,Hemotoxins(coagulants, hemorrhagins, hemolytics),Myotoxins, Cytotoxins, and Nephrotoxins.

The outcome of snake bites depends on numerous factors, including the species of snake, the area of the body bitten, the amount of venom injected, and the health conditions of the person. Feelings of terror and panic are common after a snakebite and can produce a characteristic set of symptoms mediated by the autonomic nervous system, such as a racing heart and nausea.

1. **Neurotoxins :-**produce neuromuscular paralysis ranging from dizziness to ptosis; to ophthalmoplegia, flaccid facial muscle paralysis, and inability to swallow; to paralysis of larger muscle groups; and finally to paralysis of respiratory muscles and death by asphyxiation.
2. **Coagulants :-**may have initial procoagulant action that uses up clotting factors leading to bleeding. Coagulants may directly inhibit normal clotting at several places in the clotting cascade or via inhibition of platelet aggregation.

In addition, some venom components may damage the endothelial lining of blood vessels leading to hemorrhage. Bite victims may show bleeding from nose or gums, the bite site, in saliva, urine, and stools.

3. **Myotoxins :-**can directly impact muscle contraction leading to paralysis or cause rhabdomyolysis or the breakdown of skeletal muscle. Myoglobinuria, or a dark brown urine, and hyperkalemia may be noted.
4. **Cytotoxic :-**agents have proteolytic or necrotic properties leading to the breakdown of tissue. Typical signs include massive swelling, pain, discoloration, blistering, bruising, and wound weeping. Sarafotoxins, which are found only in burrowing asps of Afro-Arabia, cause coronary artery constriction that can lead to reduced coronary blood flow, angina,and myocardial infarction.
5. **Nephrotoxins :-**can cause direct damage to kidney structures leading to bleeding, damage to several parts of the nephron, tissue oxygen deprivation, and renal failure.

Venom of snake

1. Proteolytic enzymes

   Digest the proteins and prevent the clotting of blood lead to bleeding .
2. Amino-acid oxidase

   Cause disturbance in the tissues structure and function and numbers of essential enzymes this disturbance mainly occur in the vascular system .
3. Phospholipase (A ,B , C , O)

   Act this enzymes of lysis of RBCs membrane this lead to damage and un able to act on function this can cause anemia .
4. Hydrondase

   This cause diffusion of toxin compound in body .
5. Protease

   This produce compounds the cause bleeding and lysis large numbers of simple peptide , amines , change in the cell structure and loss function .
6. Phosphodisterase

   The lead to decrease blood pressure .

Veterinary Toxicology

Snakebite Treatment

Three general principles for every bite should be kept in mind:

Snake venom poisoning is a medical emergency requiring immediate attention and the exercise of considerable judgment.

The venom is a complex mixture of substances of which the proteins contribute the major deleterious properties, and the only adequate antidote is the use of specific or polyspecificantivenomwith specific supportive therapy. Not every bite by a venomous snake ends in an envenomation. Venom may not be injected.

Widow Spiders

Mechanism of action

Widow-spider venom is a complex mixture of about six neuroactive proteins; there are also some proteolyticenzymes. The principle toxin for mammals is α-latrotoxin, a polypeptide that causes a large release and then depletion of acetylcholine and norepinephrine atthe periphery.

Treatment :-

Is largely symptomatic with control of pain byopioids and use of muscle relaxants such as diazepam andmethocarbamol to control the muscle rigidity.

Scorpion Sting

Mechanism of action

All scorpions can deliver an envenomating sting (Keegan, 1980). Scorpion venom components vary greatly between genera and may even differ based on geographic location within species. The venom consists of a mixture of low molecular weight polypeptides. At least two potent neurotoxins have been identified:

- ***α*-scorpion toxin**found in*Androctonus*,*Leiurus*, and*Buthus*spp.
- ***β*-scorpion toxin**found in*Centruroides*spp.

(Both toxins can be found in the venom of*Tityus*spp).

Thesevenoms block the voltage-sensitive sodium and potassium channels in nerves.

Clinical Signs

Scorpion stings cause instant, sharp pain at the site ofenvenomation. Some stings will cause localized pain thatresolves over hours. Localized edema and pruritus arecommon.Regional lymph nodes may enlarge, there may be anallergic reaction characterized by swelling of the eyelids,tongue, and vomiting. Sloughing of the skin at the site ofenvenomation can also occur.Signs usually resolve within 24 h*Systemically*,signs can vary but generally include numbness of face,myalgia, tachycardia or bradycardia, respiratory depression,and seizures.

Treatment

The treatment of scorpion stings, in most cases, consistsof analgesics and localwound care. Systemic signs aretreated symptomatically with control of hypertension, heartrate changes, and neurologic signs.

Ticks

Ticks are well known as being vectors for a large numberof human and animal diseases, 43species of ticks from nine different genera have been associatedwith tick paralysis:*Amblyomma,Argas,Dermacentor,Haemaphysalis,Hyalomma,Ixodes,Ornithodoros,Otobius*, and*Rhipicephalus.*

Mechanism of action

The exact mechanism(s) of action of tick toxins is(are) notwell known, but in most tick species it is suspected thatthe toxin interferes with the synthesis and/or release ofacetylcholine at the neuromuscular junctions,Causing paresis and paralysis.

Toxicity

Tick paralysis has been reported in a large variety of animalspecies, including dogs, cats, cattle, sheep, goats, llamas,poultry, wild antelope, bison, foxes, wolves, mice,ground hogs, black-tailed deer, and several species of wildbirds.

Veterinary Toxicology

Clinical signs

Include an ascendingataxia that progresses to paresis and flaccid paralysis.Early in the intoxication, animals remain bright, alert, andable to eat and drink if properly supported. Eventually,paralysis of the respiratory muscles leads to respiratoryfailure and death.

Treatment

The main goal of treatment is to remove the ticks and providesupportive care (especially respiratory support) untilrecovery occurs. Recovery can occur quite rapidly followingcomplete removal of the ticks, or it may take a fewdays

The use of topical insecticides mayaid in the removal of ticks, and can be especially helpful incases where numerous ticks are embedded. Heavily coatedanimals may need to be shaved in order to ensure thatall embedded ticks are found and removed. Removal ofembedded ticks should be performed carefully to avoidexpressing additional toxin into the wound or leaving thehead embedded in the skin. Forceps may be used to graspthe tick as close to the skin as possible and gentle tractionshould be used to remove the tick.

In most cases whereticks are removed before bulbar paralysis has occurred,the prognosis for full recovery is very good. A short-termimmunity develops following recovery from tick paralysis.

Veterinary Toxicology

Household and Industrial Products

The most household products are relatively safe and largely inaccessible to companion animals .the most products available in homes are antifreeze (containing ethylene glycol) , cleaners and disinfectants .

1. Ethylene Glycol

It's a dihydric alcohol widely used as antifreeze and coolant for automobile engines , industrial solvent and rust removal . Its pure form odorless , syrup , sweet tasting (most danger due its sweet taste) .

Exposure :-

Its relatively common occurrence in dogs , cats , swine and poultry . Its seasonally occurrence when anti-freeze is commonly used . Ethylene glycol is readily absorbed from GIT and rapidly distributed to the tissues , much of it excreted unchanged in the urine .

Mechanism of Toxicity

1. The intact ethylene glycol crosses the blood brain barrier and exerts narcotic or euphoric effects , such as those seen with ethanol .
2. Metabolism of the glycol to several acidic intermediates causes to CNS , heart , metabolic acidosis and finally kidney damage .

Toxicity

1. Ingestion sufficient amount can be fatal if untreated .
2. The margin between a single toxic dose and the lethal dose is narrow (1 : 2) .
3. The lethal dose for cat is 2 – 4 ml / kg , while 4 – 5 ml / kg in dog .
4. Poultry intoxication occurs at dosage 7 – 8 ml / kg .
5. The gross lesion of ethylene toxicity includes gastritis (hemorrhagic) , enteritis , pulmonary edema and pale swollen kidney .

Treatment

1. Activated charcoal (decontamination) .
2. Ethanol 20 % (competitive inhibitor) in cat , while in dog the 4 – methylpyrazol is (4MP) is a potent alcohol dehydrogenase inhibitor .
3. Sodium bicarbonate (correct acidosis) .
4. Saline 50 % and glucose 5 % (establish urine flow) .

2. Phenols

Found in antiseptics , germicides , household cleaners and disinfectants . Most phenols are readily absorbed from GIT , limited through intact skin . Excretion is primarily via urine .

Mechanism of Toxicity

1. Direct irritation :- direct protoplasmic effect (coagulate necrosis).
2. Accumulation in liver and kidney causing renal tubular necrosis .
3. Stimulation of respiratory center leading to hyperventilation .

Toxicity :-

The oral LD50 is 500 mg/kg for most animals , cat more sensitive than other animals due to lacking glucuronic acid .The most appear lesions are necrosis of skin and upper alimentary tract , swollen, pale kidney and hepatic necrosis (mottled liver) .

Treatment

1. Oral exposure :- charcoal , saline egg white (decontamination and dilution of phenol) .
2. Dermal exposure :- Bathing with liquid dish soap and applying glycerol .

Veterinary Toxicology

Detergents

Types

1. Anionic detergents include sulfonated or phosphorylated hydrocarbons (laundry).
2. Nonionic detergents include alkyl and aryl polyether ,sulphates , alcohols , polyglycol ethers , polyethylene glycol and sorbitanmonosttearate . Fond in soap and laundry and dishwashers detergents .
3. Cationic detergents are quaternary ammonium often contains a halogen e.g. benzalkoniumchloride .

Exposure

Careless use , but the significant problems develop due to massive exposure .

Mechanism of toxicological damage

Directly irritate the skin and mucous membranes .anionic detergents causes irritation with removal of natural oil and can result in thickening of skin , along with weeping , cracking , scaling and blistering .

Toxicity

Soaps and detergents are slightly to moderately toxic , except the automatic dishwashing detergents (extremely alkaline) . hyperemia , edema and ulceration of affected area .

Therapy

1. Feed :- Milk , water or a weak acid (vinegar) making dilution and neutralization .
2. Soap cause counteract local cationic exposure .
3. Oral exposure :-
    a. Emesis and Gastric lavage are contraindicated as for other caustic , corrosive agents .
    b. Milk and charcoal causes inactivation .

Veterinary Toxicology

Industrial and Commercial Toxicant

1. Petroleum Products

Sources

1. Crude (raw) oil contains high level of gasoline , naphtha and kerosene .
2. Refined petroleum products : Aliphatic hydrocarbons e.g. (methane , ethane , propane , butane , gasoline , kerosene , carbon tetrachloride , degreasing solvents) and aromatic hydrocarbons (benzene ,toluene , xylene) .

Exposure

1. Cattle and horses exposure to crude oil (contaminated food , industrial sites) .
2. Aquatic wildlife and birds (victim of environmental contaminated).
3. Small and large animals to refined petroleum products (home or commercial use) .

Mechanism of toxicological damage

1. Direct irritation to mucous membrane and skin .Upper respiratory irritation and aspiration pneumonia (due to volatile nature of crude oil and refined products) .
2. Pulmonary damage by gasoline (due to low viscosity , small amounts spread over large surface).
3. Oil can transfer microorganism into the lung cause infection .
4. Stimulation vomiting or bloat .

Toxicokinitics

Petroleum products are highly lipophilic , readily absorbed through intact skin and GIT mucosa . Aliphatic and aromatic hydrocarbons (high volatile) are readily absorbed through lungs , volatile aliphatic hydrocarbons excretion through lung .

Treatment

1. Charcoal or mineral oil cause reduction of absorption .
2. Emesis or gastric lavage is not recommended due to the volatile and irritating comp of petroleum and oil increases risk of aspiration pneumonia .
3. Bathing in warm water and mild detergent may reduce absorption in case of dermal exposure .The skin should not be brushed or braded .
4. Supportive treatment (antibiotic , IV fluid and cardiac stimulant) .
5. Bloat pressure should be removed by passing stomach tube .

Veterinary Toxicology

2. Fluoride

Sources

1. Naturally as fluoride .
2. Industry :-plants of aluminum ,steel ,fertilizers.

Forms :-NaF is most toxic and CaF is the least toxic.

EXPOSURE

1) Acute:-It is rare ,result from ingestion of sod fluoride ,sod fluorosilicate and hydrogen fluoride (HF) which is more toxic than NaF ,because it is corrosive and volatile.
2) Chronic:-mostly seen in dairy cattle(feed&water contain have a high level of fluoride).

Toxicokinitics :-

Fluoride is absorbed from GIT,96%-99% incorporated into bone slowly depleted (months- years).Non stored fluoride easily excreted by glomerular filtration.

Mechanism of toxicity :-

Excessive amounts result in delayed and impaired mineralization of the teeth (brown or black discoloration)and skeleton (exostosis. Osteoporosis).

Treatment:-

1) Aluminum sulphate ,aluminum chloride, calcium aluminate ,are recommend to decrease absorption of fluoride. It is ineffective once dental&skeletal lesions developed).
2) Ca-gluconate injection to increase calcium level in blood.
3) Ca-gluconategel for HF skin exposure (treatment corrosive skin lesion).

3. Polybrominated Biphenyls (PBBs)

These are man-made chemicals that have fire retardant properties , persistent in the environment and poultry .

Mechanism of toxicological action

PBBs are believed to activated RNA synthesis in the nucleus and lead to induction mono-oxygenaseenzymes .

Toxicity

Toxicosis in dairy at dosage exceeding 50 mg/kg B.W . include decreased milk production , lameness , excessive hoof growth , infertility , abortion , hematomas subcutaneous , abscesses , alopecia and wrinkling and thickening of skin .

Treatment

No useful treatment , disposal of the contaminated animals .

4. Polychlorinated Biphenyls (PCBs)

They are similar in structure to DDT , chemical inert (not hydrolyzed by water , resist alkalis , acids and corrosive chemicals) , persistent in the environmental an in food chain , where they concentrated in fish – eating birds .

Sources

1. Nonflammable oil in electrical insulation .
2. Plasticizers , paints , flame retardants and silo sealants .
3. Chemical oxidizing inhibitors .

Exposure

1. Acute and sub-acute diseases and death of cattle from contamination oil in a cattle oiler .the dosage of 2 – 10 g/kg B.W. in mammals cause acute toxicity .
2. Contamination of rice in japan in 1968 affected both chickens and humans (Yusho disease in human) , PCBc contamination produced dark pigmentation of the nails and skin , acne , swelling of the limbs jaundice , peripheral neuropathy , fever , vomiting and diarrhea . infant from mothersexposure to exposed to excessive PCBs during pregnancy are cola colored .

Treatment :-There is no specific treatment .

Prevention

Contaminated animals should never be recommended for human consumption .

Veterinary Toxicology

5. Triayl Phosphate and other Neurotoxic Phosphate Esters

Sources

Fire retardants , solvents , stablilizers , rubber or plastic , gasoline additives and plasticizers.

Exposure

1. Human :-By ginger extract contaminated with tri-orth-cresylphosphate esters , causes jumaica ginger paralysis .
2. Cattle :-Occasionally by lubricants containing tri-orth - cresylphosphate .

Mechanism of toxicity

1. Organohosphorus esters inhibit acetylcholinesterase(AchE) .
2. Enter the nervous system and cause demylination(irreversible lesion) .
3. Inhibition neurotoxic esterase (maker of potential damage) . Chicken are used as test animals .

Toxicity

Single doses or repeated small doses can induce toxicosis but depends on compound structure :-

1. Delayed neurotoxicity (phosphonates) .
2. Don't cause delayed neurotoxicity (phosphonothionates) .

Susceptibility

1. Chicken ,pheasant , young chicken (less than 10 months) are resistant .
2. Cats , cows , lambs , adults sheep and water buffalo are susceptible .
3. Rat,mice,dog , guinea pig and hamster are resistant .

Treatment

No antidote is available but prevention by avoiding potential sources is the best .

Veterinary Toxicology

Feed-Associated Toxicants

1. Ammoniated feed:

The terms bovine bonkers, bovine hysteria and ammoniated feed syndrome used to describe hyperexcitability in cattle after ingestion of toxic ammoniated hay and ammoniated liquid.

Sources:

Ammoniation is a process by which feed stuffs are treated by anhydrous ammonia to:-

1. Increase the protein content.
2. Increased palatability and digestibility of crude protein.

Toxicity:

Excessive ammonia main factor to the formation toxin (pyrazine, methylimidazole).

Clinical signs:

The syndrome of hyperexcitability has included the following symptoms: nervousness, rapid blinking, involuntary ear twitching, dilation of the pupils, trembling, ataxia, rapid respiration, salivation, apparent impairment of vision,frequent urination and defecation, frothing at the mouth, sweating, bellowing, convulsions, and stampeding, with normal behavior between episodes.

Treatment:

Many animals exhibiting symptoms have not responded to any treatments. Calves treated with acepromazine and thiamine hydrochloride . Removal of the suspect feed should be done as soon as possible.

2. Gossypol:-

Gossypol is a natural phenol derived from the cotton plant (genus Gossypium). Gossypol is a phenolic aldehyde that permeates cells and acts as an inhibitor for several dehydrogenase enzymes. It is a yellow pigment.

Source of poisoning due to using cottonseeds after harvested as feed (cottonseed meal CSM) contain high protein and high oil, so contain gossypol is yellow polyphenolic pigment found in all part of cotton but concentrated in seeds. Gossypol is cardiotoxin and antifertility agent.

Mechanism of action:

In general not fully understood. Cardiotoxic effects of gossypol are:-

1. Gradual destruction of the cardiac musculature.
2. Interference with conduction system by affecting on movement potassium K+across cell membrane.

Clinical signs:-

Two syndromes affect the heart. One is sudden death in animals that were believed to be healthy. Lambs that died suddenly were often misdiagnosed as "overeating." The other syndrome is a chronic the animals gradually become anorexic, develop a rough hair coat, become chronic poor-doers, and die .

Treatment: -

No antidote or treatment for gossypol toxicosis is available. The feed source that contains CSM should be removed immediately along with any other stress factors.

3. Non protein nitrogen: - (NPN)

Ammonia toxicosis and urea poisoning are names used for the disease caused by over consumption of non-protein nitrogen.

Sources: -

Non protein nitrogen includes all nitrogen sources that are not part of a polypeptide.Urea that addsto feed is the most common source, other sources urea phosphate, ammonium polyphosphate and ammonium salts.Livestock may also be exposed from consuming ammonium or urea-containing fertilizers.

Toxicity:-

The toxicity ofNPN due to ammonia production depleted α-ketoglutarate needed to run the citric acid cycle resulting in the inhibition of the cycle this lead to increase lactic acid (acidosis) and decrease in ATP production. Neurotoxicity is found with ammonia toxicosis.

Clinical signs:-

Signs in ruminants seen between 20 minute and 4 hours after ingestion (20 to 60 minute in cattle or 30 to 90 minutes in sheep) progression of signs are rapids. Signs are uneasiness, muscle and skin tremors (face and ears) dyspnea, frequent urination and defecation, stiffness of the legs and prostration. Other signs are colic, rumen atony.

Treatment:-

Treatmentof ammonia toxicosis is often impossible because of rapid progression of clinical signs but may be giving:

1. 5% acetic acid to decrease the pH (2 to 8 Liter given in cattle, 0.5 to 2 Liter in sheep and goats).
2. Cold water (up to 40Liter & 0oC to 4oC) to decrease temperature of the rumenlead todecreasing the activity of urease and diluting the contents of the rumen.
3. Rumenotomy to replace rumen contents hay slurry.

4. Sulfur:-

Excessive sulfur intake can result in polioencephalomalacia(PEM) in ruminants.

Sources:

1. Sulfur is an essential nutrient that is generally consumed within organic complexes.
2. Most sulfur in the body is in protein, so sulfur deficiency is nearly same with protein deficiency.
3. Monogastric animals consume sulfur containing amino acids (cysteine and methionine).
4. In ruminants microbial synthesis of protein and vitamins lead to production inorganic sulfur(sodium sulfate, magnesium sulfate, ammonium sulfate).

Veterinary Toxicology

Toxicity:-

Most of the adverse effects if sulfur toxicosis appears to result from excessive production of sulfide the ruminalmicroflora.

1. Sulfide inhibits cellular respiration.
2. Sulfide Inhibits energy metabolism of neurons and that causes neuronal necrosis.

Clinical signs:-

Signs of sulfur associated PEM include visual impairment, ear twitching and drooping, lethargy, anorexia, recumbency, convulsions, coma and death.

Treatment:-

1. Supportive therapy.
2. Thiamine injection.
3. Removal the source of sulfur intoxication.

Veterinary Toxicology

Plant poisoning

Tropane Alkaloids

Sources.

*Datura*spp. (Jimson weed, Angel's trumpet) occurs as a weed in gardens, crop fields, and dry lots where livestock are confined .*Datura*grows best in fertile soils often located in the eastern half of the United States.*Atropa belladonna*(belladonna) grows throughout the United States and is cultivated in gardens.

Toxicokinetics.

Belladonna alkaloids include atropine, hyoscyamine, and hyoscine.*Datura*contains hyoscyamine, atropine, and scopolamine. The toxic level is 0.15 mg/kg body weight of alkaloid. Cattle may be killed from ingestion of plants at 0.06% to 0.09% of body weight.

Mechanism of Action.

These alkaloids are anticholinergic, causing a parasympatholytic action. They are competitive antagonists of acetylcholine at muscarinic cholinergic receptors.

Toxicity and Risk Factors.

Although the toxin is present in all parts of the plant, it is most concentrated in the seeds.*Datura*(Jimson weed) is unpalatable and is eaten only by hungry animals.

Clinical Signs.

Pigs are most frequently affected, but all species are susceptible. Initially animals show thirst and have flushed skin. Second, they develop mydriasis and have visual disturbances resulting in insensible wandering or blindness. Restlessness and muscular twitching progress to incoordination, paralysis, and delirium (hallucinations). Respiratory paralysis may occur and results in death. At low doses, signs are parasympatholytic: dry mucous membranes, gastrointestinal atony and tympany, tachycardia, convulsions, and a reduction in urine output.

Treatment.

Treatment is limited to controlling the signs of the animal. Mania can be controlled only with tranquilizers (diazepam or phenobarbital) or anesthesia (pentobarbital). Occasionally large doses of parasympathetic drugs may be of use.

Glycosides

Calcinogenic Glycosides

Sources.

Several members of the Solanaceae family contain vitamin D–like compounds.*Solanummalacoxylon*is the calcinogenic plant responsible forthe disease. Solanaceous plant that has caused enzootic calcinosis of livestock.

Mechanism of Action.

The calcinogenic plants contain a glycoside of 1,25-dihydroxycholecalciferol (calcitriol) or a calcitriol-like compound. Calcitriol is the active form of vitamin Dand acts to increase calcium absorption from the gastrointestinal tract, increase bone resorption of calcium, and decrease renal calcium excretion.

Clinical Signs.

Cattle, horses, sheep, goats, and pigs have been affected. The disease is progressive, and may take weeks to manifest. Early signs often go unnoticed. At later stages, animals exhibit depression, weakness, weight loss, stunted growth, infertility, anorexia, cardiac arrhythmias or tachycardia, impaired or stilted gait, walking or grazing on knees, and frequent recumbency.

Treatment.

Animals should be removed from the plant source and given clean feed. Any supplemental vitamin D preparations should be discontinued. Individual treatment of animals to decrease serum calcium and phosphorus, such as the use of furosemide, prednisolone, saline diuresis, and calcitonin , is usually not practical in herd situations.

Veterinary Toxicology

Cardiac Glycosides

Sources.

Oleander*(Neriumoleander)*is an ornamental evergreen shrub with leathery, dark-green leaves . A native of the Mediterranean region, the bush is a member of the Apocyanacea family. Other plants that contain cardiac glycosides include foxglove*(Digitalis*spp.), some species of milkweed*(Asclepias*spp.), and*Kalanchoe*spp.

Mechanism of Action

Cardiac glycosides cause poisoning by inhibiting Na+/K+ ATPase, which is essential for cardiac function. This effect is similar to that of digitalis glycosides. Animals ingesting oleander plant material also suffered from central (bleating and convulsing) and peripheral nervous system effects (tremors).

Clinical Signs.

Animals exposed to oleander are often found dead. If found alive, they present with rapidly developing, nonspecific signs that may resemble colic. Clinical signs, if observed, develop 2 to 8 hours after exposure and may include abdominal pain, weakness, rumen atony, vomiting in some species, and excessive salivation. Initially, bradycardia may be present for up to 24 hours, followed by a weak, irregular, fast pulse with tachycardia and ventricular arrhythmia.

Treatment.

Exposed animals should be removed from the source. Very early after exposure, the gut should be evacuated using emesis (if appropriate). Otherwise, adsorption of the toxin using activated charcoal has been suggested. The use of potassium in fluids should be used only if hyperkalemia is demonstrated to be absent.

Veterinary Toxicology

Cyanogenic Glycosides

Sources.

Cyanogenic glycosides are found in pitted fruits in the*Prunus*genus (cherries, peaches, almonds, and apricots),inunpitted fruits, grassesand corn.

Toxicokinetics.

Once cyanogenic glycosides, such as amygdalin and prunasin, are converted to cyanide, they are rapidly absorbed from the gastrointestinal or respiratory tracts.

Mechanism of Action.

Cyanide combines with iron in cellular cytochrome oxidase to prevent terminal electron transfer and blocks cellular respiration so that oxyhemoglobin cannot release oxygen for electron transport in the cytochrome system.

Clinical Signs

Signs develop quickly, often within 10 to 60 minutes. Principal signs from acute cyanide intoxication include hyperventilation, decreased blood pressure, hypoxemia-induced convulsions, coma, shock, respiratory failure, and death.

Treatment

Optimum treatment is rapid administration of either sodium nitrite or methylene blue . Both should not be administered. The purpose of either nitrite or methylene blue is to create methemoglobin, which removes cyanide from the cytochrome oxidase to form cyanmethemoglobin. Administering 20% thiosulfate solution intravenously provides sulfur donors.

Veterinary Toxicology

Environmental Pollution with Toxicants

Agents in our surroundings that are harmful to human and animals health. Some substances, such as air and water pollutants, are recognized for their toxicity. No one would knowingly breath air polluted with sulfuric acid or drink water containing pesticides. However, other toxic agents equally harmful to human health (food additives and contaminants, bacteriotoxins, fungitoxins, phytotoxins, household products, and industrial chemicals) often go unrecognized for their serious toxicity.

Types and Causes of Pollution

The term pollution refers to the act of contaminating ones environment by introducing certain hazardous contaminants that disturb the ecosystem and directly or indirectly affect the living organisms of that ecosystem. Pollution in general is the activity of disturbing the natural system and balance of an environment.

Sources of chemical in the environment :- contamination of the environment may be :-

1. Industrial :- e.g. phosphate of detergents used in the clothes laundry is nutrient source of algae and other organisms .
2. Agricultural :- e.g. pesticides applied directly to soil to control insects , wood , plant diseases . some of these chemicals can persist for many years and their potential movement from soil into water and from both water into organism in and on water and soil . these effects of pesticides in food chain .
3. Domestic and urban :- e.g. lead contamination of soil and occasionally water near highways result from the use of tetraethylead as an antiknock component of gasoline for automobile . e.g. water fluoridation to prevent tooth decay , but excessive concentration of fluorine can result molting and discoloration of teeth .e.g. purification water results chlorination of certain hydrocarbons that are potentially carcinogenic .
4. Naturally occurring e.g. naturally occurring arsenic in copper ores , frequently find its way to soil and water .

Veterinary Toxicology

There are many types of pollution, but three of them have the most perilous effect on our lives. Following are the three most dangerous types of pollutions and their causes:

Air Pollution

Air pollution is perhaps the most common and the most dangerous type of pollution. It involves the direct release of chemicals into the environment. The chemicals then become the part of the air around us that all the living things take in. The increase in the rate of diseases such as asthma and lung cancer today is due to the increase in the air pollution around us. Air pollution is also a cause of global warming and acid rain.

Causes of Air Pollution

Basically the air pollution is caused by the burning of fuel that directly releases hazardous chemicals into the air. For example the burning of coal releases sulphur dioxide, a poisonous gas which is responsible for acid rain. The sources of such chemicals are the large factories, smoke from the vehicles, chimneys and burning of wood.

Soil Pollution

Soil pollution involves the contamination of soil by the release of harmful substances into the soil. Unlike air pollution, which has a direct effect on human lives, soil pollution causes an indirect damage to humans and other animals.

The lives of all the living things depend on three sources: water, light and soil. The plants which are the producers of the food chain take up their nutrients, which are essential for their living, from the soil.

The nutrients taken by the plants are then transferred to the consumers that depend on these plants. Hence a soil consisting of contaminants will not only affect the plants growing on the soil but it will also indirectly harm the entire food chain.

Causes of Soil Pollution

Soil pollution is mainly caused by the release of industrial waste. This waste is directly incorporated into the soil by large industries and factories. Soil pollution is also caused by human acts as mining and deforestation etc.

Water Pollution

The 75% of the earth's surface is covered with water and more than half of the total population of earth's species resides in water. Moreover, our life greatly depends on water and life without water is impossible. Water pollution not only affects the fish and animals living in the water but also affects the whole food chain by also transferring the contaminants to the consumers depending on these animals. Water used from a polluted lake directly contaminates its user. Many of the water creatures are on the verge of extinction due to the dramatic increase in the water pollution.

Cause of Water Pollution

Just like air and soil pollution, water pollution is caused by the direct incorporation of hazardous pollutants. The sources of these pollutants are yet again the large industries and factories that dispose of their waste in lakes and ponds.

Environmental Effects

Vegetation:

Pollutants may visibly injure vegetation by bleaching, other color changes, and necrosis, or by more subtle changes such as alterations in growth or reproduction. Air pollution can also result in measurable effects on forest ecosystems, such as reduction in forest growth, change in forest species, and increased susceptibility to forest pests. High-dose exposure to pollutants, which is associated with point source emissions such as smelters, frequently results in complete destruction of trees and shrubs in the surrounding area.

Domestic Animals :

Although domestic animals can be affected directly by air pollutants, the main concern is chronic poisoning as a result of ingestion of forage that has been contaminated by airborne pollutants. Pollutants important in this connection are arsenic, lead, and molybdenum. Fluoride emissions from industries producing phosphate fertilizers and derivatives have damaged cattle throughout the world. The raw material, phosphate rock, can contain up to 4% fluoride, some of which is released into the air and water. Farm animals, particularly cattle, sheep, and swine, are susceptible to fluoride toxicity (fluorosis), which is characterized by mottled and soft teeth, and osterofluoritic bone lesions, which lead to lameness and, eventually, death.

Veterinary Toxicology

Pharmaceuticals

Analgesics

Non-steroidal Anti-inflammatoryAgents

Mechanism of Action.

These compounds reduce inflammation by inhibiting the cyclooxygenase (COX) enzyme system. COX mediates the production of cyclic endoperoxides from arachidonic acid to yield prostaglandins.COX1 and COX2, which are encoded by different genes, aretwo different isoforms of the COX enzyme.

Toxicity

Non-steroidal anti-inflammatory agentsare prevalent and arefound in most households, thus posing asignificant exposure potential to pets. Animals may becomepoisoned by accidental ingestion (more common in dogs) orinappropriate administration by owners. The long-term useof NSAIDs in themanagement of orthopedic disease predisposessome animals to the development of toxicosis.

Clinical Signs

1. The initial sign is an altered respiratory pattern.
2. Theanimal may vomit early in the clinical course with depression, hyperthemia, dehydration,and, sometimes, seizure activity.
3. Acute intoxication by other NSAIDs isgastrointestinal distress with signs that include nausea,vomiting, hematemesis, melena, anorexia, and colic.
4. Clinicalsigns associated with nephrotoxicosis include an acute onsetof oliguria.
5. Animalssuffering from thehepatotoxic syndromemay present with anorexia, jaundice, hepatic encephalopathy,coagulopathy, or ascites.

Treatment

1. No specific antidote is available for NSAID intoxication .
2. the treatment is symptomatic and supportive, includesemesis,for a recent ingestion.
3. Activated charcoal and sorbitol cathartic (Toxiban) administration is necessary to adsorb any of thedrugsremaining in the gastrointestinal tract.
4. Fluid therapy is indicated in the poisoned patient to maintain renal function and urine flow.
5. Urinary alkalinization using sodium bicarbonate may increase the elimination of aspirin.

Barbiturates

Synonyms

Several classes of barbiturates and relateddrugs are used in the treatment and prevention of seizures.Phenobarbital (long-acting) and pentobarbital (short-acting)are two of the more commonly used barbiturate agents.

Toxicokinetics:-Phenobarbital exhibits enterohepatic recycling.

Mechanism of Action

The therapeutic effects of thebarbiturates relate to their ability to increase the binding ofgamma-aminobutyric acid (GABA), the major inhibitorneurotransmitter of the CNS, to its receptor. This results ina greater influx of chloride into the cell, causing hyperpolarizationand decreased excitability.

Clinical Signs

1. Clinical signs associated with an acutetoxicosis include shallow respiration, incoordination, lethargy,coma, loss of reflexes, anddilated pupils.
2. Clinical signsassociated with hepatotoxicosis include icterus, depression,and ascites.

Treatment

1. Decontaminationincludes repeated administration of activatedcharcoal every 4 to 6 hours.
2. A saline cathartic isoften beneficial because of the reduction of gastrointestinal motility and subsequent constipationthat is often noted with barbiturate administration.
3. Increased elimination of the barbiturates may be achievedby alkalinization of the urine with sodium bicarbonate.
4. Symptomatic therapy includes maintenance of a patentairway with intubation and oxygen therapy.

Antimicrobials

Sulfonamides

Synonyms

Some of the more common sulfonamidesinclude sulfadimethoxine, sulfadiazine, sulfamethazine, sulfaquinoxaline,sulfathiazole, sulfamerazine, sulfasalazine, andsulfachloropyridazine.

Sources

A wide variety ofsulfonamides are used to treatbacterial infections and to prevent coccidiosis. Sulfaquinoxalineis used as an adjunct in some anticoagulant rodenticideproducts. Additionally,several of the sulfonamides arecombined with trimethoprim to produce the potentiatedsulfonamides that exhibit a broader antibacterial spectrum.

Mechanism of Action

The mechanism of toxicosis relates to thephysiochemical properties of these drugs, their actions onnormal bacterial flora, or the ability to elicit hypersensitivityreactions. The development of crystalluria is due to thedecreased water solubility of the parent compound ormetabolites (especially acetylated metabolites). The parentcompound or metabolite becomes less soluble in theglomerular filtrate and precipitate in the renal tubules,causing renal damage.

Clinical Signs

Animalsmay present with signs of acuterenal failure or urinary tract infections, specifically oliguria,anuria, hematuria or crystalluria. Animals may also exhibitsigns of coagulation abnormalities including subcutaneousbruising or prolonged bleeding from wounds.

Treatment

1. The initial step in therapy is to discontinue theuse of the offending agents from all sources, including therapeutic sources, feed, or water.
2. Fluid therapy is indicatedin the dehydrated or crystalluricpatient.
3. Increased eliminationof the sulfonamide may be achieved by alkalinization ofthe urine with sodium bicarbonate.

Penicillins

Mechanism of Action

Penicillin and all of the beta lactamantibiotics exhibit antimicrobial activity by acting onthe cell wall of bacteria. Thebeta-lactams inhibit the actionof transpeptidases (penicillin-binding proteins) that form thebacterial cell wall. The mechanisms of toxicosis relate tohypersensitivity reactions, other immune-mediated reactions,or selective overgrowth of some enteric bacterial species.

Toxicity

Animals with a previousreaction to penicillin have a greater risk for subsequent adverse events. The risk oftoxicosis is also greater withvenous administration and prior antimicrobial therapy (productionof antibodies). Thetoxic syndromes associated withpenicillin may be noted with normal therapeutic doses.

Clinical Signs

1. Clinical signs associated with an anaphylacticreaction may include hemorrhagic enterocolitis orrespiratory distress.
2. Signs associated with immune-mediatedhemolytic anemia include icterus, depression, pale mucousmembranes, red-brown urine, splenomegaly, or tachycardia.

Treatment

1. The treatmentof anaphylaxis should focus onemergency and supportive care.
2. The animal's airway shouldbe maintained and oxygen provided, if necessary.
3. Epinephrine may be necessaryto maintain the vascular tone.
4. Fluid therapy may benecessary to provide sufficient volume for the cardiovascularsystem.

Tetracycline

Synonyms:-Oxytetracycline, chlortetracycline, tetracycline,and doxycycline are several types of this antibiotic.

Mechanism of Action

The mechanismsof toxicosis donot appear to be related to theantimicrobial action of the drug. One proposed mechanismfor the cardiovascular effects isdue to a propylene glycolvehicle. It is thought that the propylene glycol induceshistamine release leading to cardiovascular collapse.Another proposed mechanism for cardiovascular collapserelates to the ability of tetracycline to chelate calciumin serum acute renal failure. Hepatotoxicity may be notedwith tetracycline administration that is due to triglycerideaccumulation in the mitochondria of hepatocytes.

Clinical Signs

1. Clinical signs associated with tetracyclineinducedrenal disease include vomiting, diarrhea, dehydration,and oliguria.
2. Signsassociated with cardiovasculartoxicosis include severe hypotension, decreased heart rate,collapse, anddeath.

Treatment

1. Animals thatexhibit cardiovascular collapsemay be treated symptomatically with fluids and calciumgluconate.
2. Concurrent intravenous administration of fluidsand diuretics (mannitol and furosemide) may prevent renaltoxicosis by maintaining normalurine production.
3. Hemodialysismay be necessary if the renal function is severelycompromised.

Fluoroquinolones

Veterinary Toxicology

Synonyms

The fluoroquinolones are relatively new toveterinary medicine. Members ofthis group include enrofloxacin(Baytril, difloxacin,ciprofloxacin, and orbifloxacin (Orbax).

Mechanism of Action

The antimicrobial activity of thefluoroquinolones is due to their ability to inhibit the type IItopoisomerase of the bacteria.This prevents the coiling andtherefore the replication andsynthesis of DNA. The mechanismof action for fluoroquinolone-mediated arthropathymay be related to the ability to chelate magnesium.

Toxicity

Immature animals of allspecies are at greatest risk of developing arthropathy. There is some variability between species in this concern.Arthropathy was induced by norfloxacin at 25, 50, and100 mg/kg/day in young rabbits, dogs, and rats, respectively.Ofloxacin caused articular lesions in immature dogsat 20 mg/kg/day for 8 days.

Clinical Signs

As a class of antimicrobials, the mostcommon adverse effects are to the gastrointestinal tract(nausea, vomiting, and diarrhea) and CNS(seizures).These toxic syndromes tend to bemild and reversible. The uniqueaspect of the fluoroquinolones is the clinical picture of ayounger animal with lameness and pain of a weight-bearingjoint.

Treatment

The antibiotic should be discontinued at thefirst sign of toxicosis. Supportive therapy includes fluids tomaintain urine production and flow to increase eliminationof the fluoroquinolone.