VPC 404- VETERINARY PHARMACY AND TOXICOLOGY

INTRODUCTORY TOXICOLOGY; SOURCES AND TYPES OF POISON, ANTIDOTAL THERAPY

Instructional Objectives:

- **Terms to note in Toxicology**
- **Diagnosis and principles of treatment of poisoning**

Definitions:

- Toxicology: It is the science or study of poisons on biologic systems, including their properties, actions and effects. Also their detection and identification, the treatment and prevention of the conditions produced by them.
- Toxicant: Any poisonous agent
- Toxins/Biotoxins: Poisons produced by biologic sources e.g venom, plant toxins.
- Toxicosis/ Poisoning/ Intoxication: Any disease produced by a toxicant
- Acute toxicosis: Effects during the first 24 hours
- Chronic toxicosis: Effects produced by prolonged exposure (> 3months)
- Toxicity: Refers to the amount of a toxicant necessary to produce a detrimental effect.
- Hazard: Describes the likelihood of poisoning under conditions of use.

- Toxicant accumulation/ biomagnifications: Occurs when absorption exceeds the ability of the body to destroy or excrete a xenobiotic compound.
- Ecotoxicology: The study of the relationship of potentialy toxic chemicals in living organisms and their environment.
- Tolerance: The ability of an organism to show less response to a specific dose of a chemical than it demonstrated on a previous exposure; refers to acquired and not innate resistance.
- LD_{50}: The dose that is lethal to 50% of a test sample or population. Expression of toxicant concentrations are in ppb or ppm in feedstuff, water, air, tissue etc. Other expressions of dose are maximum nontoxic dose, maximum tolerated dose, approximate lethal dose.

Toxicology as a discipline

- It is a multifaceted science
- It contributes to, and draws from fields such as chemistry, pharmacology, pathology, psychology, clinical medicine, botany etc.
- ***Is toxicology a chemical or biological science?***

Who are toxicologists?

- Toxicologists are persons trained in the knowledge of poisons.
- They may have been trained solely in this specialty or more often than not, they were trained as veterinarians, physicians, chemists, physiologists, pharmacologists, entomologists, botanists, agronomists and some other specialties.
- The common factor is an interest in learning more about the undesirable effects of substances and energies on living organisms and their environment.

Veterinary Toxicologist

- A person having special knowledge of the poisons affecting the animals and birds in which man is interested for his economic gain or pleasure, and of those substances which, when present in animal products, could injure the health of the people consuming them.

- He is also concerned with the determination of the safety of drugs, chemicals and energies intended for direct use by people (the best qualified to evaluate the results of animal experiment action which usually preceed human usage).

Environmental Toxicology

- Chemicals released into the environment abound there to elicit their deleterious effects on the ecology where man, animals and other organisms interact.
- The delicate interactions is altered by these chemicals with devastating effects on man and animals.

Factors affecting the activity of poisons

Exposure-related, biologic or chemical factors regulate absorption, metabolism and elimination and accordingly, influence the clinical consequences.

Factors related to exposure:

- Dose
- Duration and frequency of exposure
- Route of exposure
- Time of exposure
- Environmental factors e.g temperature, humidity etc

Biologic factors:

- Species of animal
- Age and size of animal
- Sex and hormonal factor of animal
- Nutritional and dietary factor
- Health status

Chemical factors:

- Chemical nature of the toxicant
- Vehicle/Carrier

Diagnosis

- History
- Clinical signs
- P/M lesions
- Laboratory examinations
- Bioassay/ Animal inoculation

Treatment of Poisoning

General Considerations:

- Each clinical case of poisoning presents individual problems
- More often than not, approach to treatment is determined by
    i. Nature of poison involved
    ii. Condition of the patient

Principles of therapy:

1. Prevention of further absorption
2. Supportive or symptomatic treatment
3. Specific antidote

Prevention of further absorption:

- Remove the source of poison or remove the animals from the area in which the poison exist.
- Limit the absorption of material already in or on the animal for topical chemicals. Wash the animal or remove contaminated hair or wool.
- For ingested toxicants**:**

- Induce vomiting eg apomorphine
- Gastric lavage is useful in smaller animals
- Rumenotomy in ruminants
- Purgatnion when slow-acting poisons are involved.
- Activated charcoal serves to adsorb poison in the stomach

Supportive Therapy:

- Control of seizures
- Maintenance of respiration
- Treatment for shock
- Correction of electrolyte and fluid balance

- Control of cardiac function
- Alleviation of pain

Specific Treatment (Antidotal therapy):

- This is application of drugs to reverse or neutralize the effect of the poison.
- Specific antidotes for the treatment of poisoning are highly desirable but rather rare.
- Some antidotes form complexes with the toxicant (e.g the oximes bind with organophosphates), others block or compete for receptor sites e.g vitamin K competes with the receptor for coumarin anticoagulants such as warfarin and a few affect metabolism of the toxicant e.g ferric to ferrous reduction with methylene blue in nitrate poisoning.

Other Examples:

i. Chloral hydrate or barbiturates for treatment of convulsions due to strychnine and other chlorinated hydrocarbons.
ii. Atropine sulphate is the antidote for organic phosphorus and carbonates poisoning.
iii. BAL or dimercaprol is an antidote for lead, arsenic or mercury poisoning.
iv. CaEDTA (Ca ethylenediamine tetra acetate) is used as a chelating agent in lead poisoning.
v. Sodium nitrate is used for cyanide poisoning.
vi. Tannic acid will precipitate heavy metals.

TOXINS OF ANIMAL ORIGIN

Instructional Objectives:

- **Snake bite/Envenomation**
- **Insect bites and stings**
- **Scorpion and spider toxin**
- **Fish toxin**
- **Treatment**

Toxins of animal origin are compounds or enzymes of definite animal species (terrestrial or marine). The origin of animal venoms might be directed by 2 principal needs of the organism.

i) nutrition
ii) defense

Venomous animals are classified into:

a. Actively venomous. These have venom glands and mechanisms for excretion or extrusion of the venoms as well as the apparatus with which to inflict the wounds or inject the venomous substances e.g snakes, bees.
b. Passively venomous. They have venom glands and venom excreting duct but without adequate apparatus for inflicting wounds or injecting venom eg toads, frogs and salamanders.

Venom is extruded to the outer world generally by biting or stinging eg shrew, serpent fishes etc. Other animals envenomate their victims by direct body contact e.g caterpillars, jellyfishes etc.

EFFECTS OF ENVENOMATION

Toxins of animals could act as

i. haemotoxin
ii. neurotoxin
iii. cardiotoxin
iv. necrotoxin

Haemotoxins

These could cause:

1. Direct haemolysis eg. mellitin
2. Indirect haemolysis- phospholipase A

Neurotoxins

These are obtained from the cobras and mambas families of snakes; it includes

i. Presynaptic toxin
ii. Postsynaptic toxin

Cardiotoxins

These are similar to digitalis in action by having similar depolarizing effects on the membrane.

VENOMS OF BEES, HORNETS AND WASPS

Insects such as bees, hornets and wasps are all closely related members of the order Hymenoptera. The high mortality rate from such stings is attributed to anaphylactic shock

resulting from hypersensitivity to venom peptide. They have highly specialized apparatus which serves for secretions, storage and ejection of venom.

Composition of Hymenopteran Venom

1. Biogenic Amines - They are of importance in the initial pain following a sting.
2. Peptides and small proteins - These include mellitin, apamine, mast cell degranulating peptide (MCD) and kinins.

i. Mellitin - It is a basic polypeptide molecular weight of 2850 having 26 amino acids in the chain. Part of the chain is electron neutral and hydrophobic while the other end (NH_2) is strongly basic and hydrophilic. Mellitin is haemolytic, it increases vascular permeability, causes muscular contraction and blocks neuromuscular transmission.

ii. Apamine - This is a basic polypeptide of 18 amino acids with 2-sulfur bridges. Its main site of action is the CNS (neurotoxic) where it causes excitatory and partly inhibitory action.

iii. Mast cell degranulating peptide - This causes the degranulation of the tissue mast cells leading to the liberation of histamine.

iv. Phospholipase A - It is an enzyme component of the bee toxin with indirect haemolytic effect through the production of lysophosphatide and destruction of thromboplastin. The phospholipase component is thought to be the cause of decrease in blood pressure after injection of bee toxin. Phospholipase A cannot on its own cause haemolysis unless with mellitin.

Direct and Indirect haemolysin: Direct-mellitin; Indirect- phospholipase A. The actions of both are said to have autocatalytic which acts on RBC with resultant lysis. This causes the accessible lecithin being released which is acted upon by phospholipase A (indirect hemolysin) to convert it into lysolecithin which reacts with the RBC. Lysolecithin has qualities of detergent and as saponin it causes lysis of biological membrane of RBC mitochondrion and lysosome.

v. Hyaluronidase and histamine - Hyaluronidase breaks down the hyaluronic acid and depolarizes the tissue matrix and by this facilitates the spread of the other toxins.

Mortality is higher with bee toxins than snake venom. Bee toxin causes desensitization leading to allergy, anaphylactic shock and death.

Treatment of bee and wasp poisoning

a. Removal of sting if available

b. Bee stings should be washed in alkaline e.g soap solution or dilute NH_3. Wasp stings are bathed in dilute acid (vinegar)

c. Use of antihistamine eg. promethazine.

SNAKE VENOM

Quantity of venom ejected depends on size and species of snake

Composition of snake venom:

a. **PROTEIN CONSTITUENTS** - About 90-95% of dry snake venom consists of toxic proteins, nontoxic proteins and enzymes. Most of the enzymes are hydrolytic e.g. hyaluronidase and this is thought to facilitate tissue damage on the prey to help eventual digestion (exodigestion). Sometimes these enzymes are employed for self defence.

i. Proteases destroy endothelium of blood vessels and lymph.

ii. Phosphatidase, lecithinase, nucleases take part in haemolysis

iii. Lecithinase attacks capillary endothelium, acts on the heart, and causes lung hemorrhages

iv. Phosphoesterases also participate in haemolysis.

b. NON PROTEIN CONSTITUENTS

i. Inorganic cations which may balance the charge on the proteins. Some of the venoms possess anticholinesterase activity which required Zn^{2+} or to lesser degree Cobalt. Moderate amount of calcium in the venom is used to activate phospholipase A2 and direct hemolytic factor.

ii. Biogenic amines such as bradykinin, histamine, 4-hydroxytryptamine, N-methytryptamine, bufotenine, serotonin are also present.

PHARMACOLOGY

Actions of snake venom are classified into;

i. Primary effects – the venom acts directly on the organs and tissues and are usually irreversible.

ii. Secondary effects- These effects are produced by substances released from tissues due to the venom. They may or may not be irreversible. The substances include

histamine, bradykinin, and unsaturated fatty acids which act primary on smooth muscles and lysolecithin which alters cell permeability.

CLINICAL SIGNS OF OPHIDIC ENVENOMATION

HYDROPHEID ENVENOMATION

WATER SNAKES

The assaulted animal senses no pain except for the initial prick. Thereafter, it develops muscular stiffness, lockjaw followed by generalized flaccid paralysis. No blood pressure changes though there is increased blood pressure towards the time of death. Terminally there is myoglobinuria, urine and fecal incontinence, sweating and respiratory failure.

ELAPIDAE ENVENOMATION

Includes the colubrides - cobras, mambas and coral snakes.

Toxin is haemolytically active, contains phospholipase A; neurotoxin which is a polypeptide with curare type neuromuscular activity which could be very dangerous because of respiratory muscle paralysis; cardiotoxin; cholinesterases. The CNS active component of cobra toxin liberate bound Ach and initiates oxidative metabolism of the brain giving an analgesic effect. The toxin also liberates adrenaline from the adrenal medulla which is responsible for the hyperglycaemic effect of the toxin.

CLINICAL SIGNS

Pain at site followed by numbness, lassitude, drowsiness comparable to alcohol intoxication followed by a sense of slight respiratory difficulty, weak pulse, tachycardia, drooping of eyelids, difficulty in bellowing, paralysis of bronchial and laryngeal muscle, coma, cessation of respiration and death.

Effect on blood coagulation

The snake venom either inhibits or promotes blood clotting. The mechanism of action as an anticoagulant is either via the activation of tissue thromboplastin or via the proteolytic destruction of the prothrombin including fibrinolysis of fibrinogen.

Its coagulant action is via the proteolytic conversion of prothrombin to thrombin or fibrinogen to fibrin.

VIPERIDAE AND CROTOLIDAE ENVENOMATION

These are the true (puff adder) and pit vipers (rattle snakes and moccasin).

The head of the crotalid is broader than the neck; the eyes have vertically elliptical cat-like pupils. The crotalids are called pit vipers due to a deep depression (pit) that is located midway between but below the level of the eye and nostril. The pit is believed to be a sensory organ than aids in detecting the proximity of prey in absolute darkness.

A pair of glands, one on either side of the head are connected to two hollow fangs each fused to corresponding maxillary bone (which is movable). The venom from these glands are believed to initiate digestion of the body of the prey through enzymatic action.

CLINICAL SIGNS

They produce crototoxins (neurotoxin) which contains hyaluronidase and phospholipases. The snake bite causes burning piercing pain at the site of wound, edema, lymphaginitis and regional lymphadenitis. As time progresses, there is petechial formation, subcutaneous gesticulation and hematoma at the region of bite.

Diffuse haemorrhages resulting in epistaxis, hemetemesis and haematura. Neurotoxic activities are seen with vagal paralysis, weakening of accommodation.

In severe cases, there is vomiting, urinal and faecal incontinence, dropping of blood pressure leading to shock. Acute circulatory collapse and death soon ensues.

Occurrence of snake envenomation in animals

Of all animals, dogs by far suffer from snake bites as dogs frequently attack snakes and are bitten on the neck or head. Cats tend to avoid snakes and they appear resistant to snake venom.

Farm animals are more likely to be bitten on the limbs and grazing animals are likely to be bitten on the lips or jaws. Due to their size, venoms tend to be less fatal in large animals though it is always not the rule. In decreasing order, the sensitivity to snake venom is horse, sheep, ox, goat, dog, pig and cat.

DIAGNOSIS

The diagnostic factor is the presence of fangs marks which are seen in the centre of a swollen area.

TREATMENT

The most important is the speed of action taking towards the treatment. First aid is important.

1. Application of a tourniquet though its use is doubtful in case of vipers which induces local edema.
2. Incision and suction - Incision should be small and suction should be by cupping. Mouth suction carries the risk of envenomation.
3. Life saving treatment
    a. Use of the correct antivenin obtained from the horse immuned against the correct snake. Problem of identifying a correct snake.
    b. Polyvalent serum administered IM or IV for serious cases.

    In case of vipers some of the serum has to be infused around the bites.

    Cortisone and similar steroids increase the survival rate and enhance the action of the serum and should be combined only with polyvalent serum.
4. Introduction of saline and calcium borogluconate is also useful.
5. Pethidine is adequate for alleviating pains
6. Antibiotic therapy may be required in cases of suspicion that fangs are contaminated.
7. Horses normally show edema of the throat and nasal region when bitten on the head and this may necessitate tracheotomy.

SCORPION VENOM

Unlike snakes, all scorpions are venomous. The venom is injected by means of a stinger found at the tip of the telson, the terminal structure of the tail.

Composition

1. Enzymes - Phospholipase A, anticholinesterase, hyaluronidase, phosphomonoesterase, nucleotidase, gelatinase and protease.
2. Non-protein components - Biogenic amines such as histamine, 5HT and tryptamine

CLINICAL SIGNS

Pain, local edema and fever 1-20 hours after sting, sweating, pallor, restlessness, anxiety, salivation, nausea, abdominal cramps. Sensation of choking, muscle weakness and twitching. Initial tachycardia changes to bradycardia and initial hypertension to hypotension. There is

respiratory distress and subsequent cyanosis. Death results from cardiovascular collapse and pulmonary oedema.

TOAD TOXIN

The cutaneous secretion contains toxins and some of them are steroids. They are

1. Bufotoxin
2. Bufogenin

The bufotoxins have adrenaline like effect. The bufogenin called bufodienolides, in structure have digitalis-like action. Other toxic components are base of hydroxyl-tryptamine, derivatives of bufotannin bufottenidine, bufoforthron. Some of them may contain adrenaline and some in addition contain hemolysin agglutinating components with local irritating compounds. The hydroxytryptamine derivatives are indoles acting similar to 5-hydroxytryptamine by lowing the blood pressure. They stimulate the uterine muscles, have nicotine like effect and inhibit cholinesterase eg amino oxidase.

TREATMENT

a. Wash the area
b. Treatment with atropine which is a specific antagonist
c. Sedation with sodium pentobarbitone
d. Administration of an analeptic to counteract depression eg laptazol
e. Artificial respiration.

SPIDER VENOM

Black widow spider (*Lactodectrus mactanus*)

COMPOSITION

Toxic proteins or necrotoxin

1. Enzymes – hyaluronidase, proteases
2. Non protein components- histamine and 5HT

Its venom is about 15 x as poisonous as that of rattle snakes.

Dogs are frequently affected and it is often fatal.

CLINICAL SIGNS

Extreme pain, emesis, rigidity abdominal muscles, jelly like oedema at region of bite, weakness, dyspnoea followed by paralysis. In acute cases, death occurs in 4-6 hours.

Spider bites are differentiated from snake bites by the absence of fang marks.

TREATMENT

If specific antivernim is not available, then an IM injection of serum of an immuned dog could be used.

Analgesic to relieve pain.

Atropine SO4

Prognosis is uncertain.

FISH TOXINS

About 40 spp of round fish are known to be poisonous. Most belong to the family Tetroodontidae. Their toxins are tetrodotoxins which are concentrated in the ovary, liver and to some extent in the intestine and skin. Some species also have their muscles being toxic. Toxicity relates to specific toxin inherent to the fish.

The shell fish produces saxitoxin whose mechanism of action is qualitatively similar to that of tetrodotoxin.

Mechanism of action of tetrodotoxin

There is selective inhibition of cellular Na ion movement. The action potential dependent on Na influx can be reversibly and actively blocked. This results in neural transmission leading to paralysis similar to that cocaine. Effect of tetrodotoxin is 100x more then that