Dr.Banan khalid Abdulrhmam, *BVMS, MSc, PhD*
Assistant Professor, Department of Physiology, Biochemistry, and Pharmacology
College of Veterinary Medicine, University of Mosul, Mosul, Iraq
https://orcid.org/0000-0002-6057-7659
https://www.researchgate.net/profile/Banankh_Al-baggou

Concepts & terminology

Toxicology:

The science of poisons and poisoning.
or
The science that deals with or study the adverse effects (toxicities) of chemicals or physical agents on living organisms under specific condition.

Clinical toxicology

It studies the diseases induced or associated with toxicants.
It is also concerned with the chemical properties of toxicants and their biological effects, diagnosis & treatment.

Poison (toxicant)

Any substance when introduced into or applied on the body can influence on the life processes of the organism.

It does not include mechanical or thermal effects.
Poison any solid , liquid or gas that interfere with the life process.

Toxin

A toxicant or poison of natural origin e.g. from insects (biotoxin), from animals (zootoxin), from fungus (mycotoxin), from plants (phytotoxin).

Toxic

A substance having a characteristic of producing an undesirable or adverse health effects.

Toxicity

The quantity of a toxicant or poison required to produce a specific adverse effects or toxic effects.
The intrinsic ability of quantity of poison under certain conditions to induce poisoning or death.

Toxicosis (poisoning)

The state of being poisoned.

Exposure:

A toxicant must come in contact with an organism.

It means by which an organism comes in contacts with the substance is the route of exposure for that chemicals. e.g. in the air, water, soil food, medications.

Dose:

The total amount of toxicants administered to an organism at a specific time intervals.

The quantity can be defined in terms per unit of body weight or per body surface area. e.g. dosage rate in dog 2 mg/kg/day.

Hazard

The likelihood of occurrence of poisoning or adverse effects under specified conditions of use.

Its qualitative nature of adverse or undesirable effects resulting from exposure to toxicants or physical agents.

e.g. asphyxiation a hazard from acute exposure to CO.

Risk

It's the quantitative probability of danger from a toxicant under given conditions of exposure.

Or the probability that specific exposure or dose will produce a toxic effects.

e.g. risk of cancer from compound X at certain exposure level is 1:1000000.

Risk= Hazard × Exposure

Safety

The probability that adverse effects will not happen.

Or will not produce toxic effects.

Side effects

The undesirable effects that results from therapeutic doses of chemicals.

It will not happen or will not produce toxic effects.

Expression of toxicity:

Minimum toxic dose (MTD)

The lowest dose that causes detectable toxic effects.

Median lethal dose (MLD50)

The dose of a chemical that causes death in 50% of test animals.

Lethal concentration (LC)

The lowest concentration of poison or drug .in food or water that cause death.

Maximum tolerable dose

The highest dose that can be tolerated by the living organism without detectable toxic effects.

Mechanism of toxic action:

The necessary biologic interactions by which a toxicant exerts its toxic effects on an organism. e.g. CO poisoning due to the binding of Co to Hb thus preventing the transport of O2 within the blood.

Duration of exposure:

Acute of exposure or toxicity

A single or multiple exposure (within or less than 24hrs) resulting in acute signs of poisoning which may end in death of the test subject.

Subacute exposure or toxicity

Repeated exposure to the compound greater than 24hrs to less than 30 days (1months). Survival time is usually longer than that of the acute poisoning.

Subchronic exposure or toxicity

Repeated or multiple exposure to the compound for 30-90 days. Additive tissue damage should be expected with this type of toxicity testing.

Chronic exposure or toxicity

Repeated or multiple exposure to the compound for more than 90 days(3 months) for up to a years.

Type of toxicologic effects:

1.Graded toxic effects.
2.Quantal toxic effects.
3.Immediate toxic effects.
4.Delayed toxic effects.
5.Local toxic effects.
6.Systemic effects.
7. Target organ effects.

Routes of exposure to the toxicants

- **Inhalation**
- **Oral**
- **Dermal**
- **Injection**

Toxicokinetics

Absorption of toxicants:

1. GIT major route.

Toxicant present in food or drinking water.

Factors affect absorption of toxicants:

Lipid solubility and molecular size, PH of stomach, Degree of ionization in the intestine.

2. Skin

All toxicants penetrate the skin by passive diffusion. Lipophilic chemicals are much better absorbed than hydrophilic chemicals.

3. Lung

Gases & vapor e.g. CO, SO2 &volatile hydrocarbons are absorbed through the lung.

Also liquid and particles of aerosols e.g. sulfuric acid aerosols or silica dust absorbed in the lung.

Note: molecule move through membrane by passive transfer or diffusion.

Facilitated diffusion, Active transport, phagocytosis and pinocytosis.

Distribution of toxicants and elimination (Disposition)

Biotransformation:

It's the process that generate intermediate compound may be toxic or more toxic than the original compound (lethal synthesis).

It have 2 general mechanisms:

The compound enter the body and modified into more water-soluble compound which can easily excreted.

Biotransformation reactions:

Phase I and phase II reactions

Phase I:

Its catabolic or break down reaction.

Oxidation , reduction, hydrolysis.

It occurs in cytochrome P450.

Phase II:

Are synthetic reactions.

Addition molecule in covalently bound to the metabolite.

Its enzyme –catalyzed conjugation of chemicals or its phase I products e.g. glucuronic acid, glutathione or sulfate.

The conjugates are more water soluble and excreted readily .

Factors influence on biotransformation

1.Species and breed.
2. Individual variation.
3. Sex.
4. Age.
5. Nutritional status.
6. Co-exposure to other chemicals.

Excretion of toxicants

1. Kidneys the most important excretory organ.
2. Liver (1st pass effects) enterohepatic circulation in to the bile.
3. Lung (pulmonary excretion).
Other routes:
Skin, hair, sweat, nail, milk.

Total management of toxicological problem

1. Stabilization
2. Prevent further absorption of poison.
3. Diagnosis and antidotal procedures.
4. Enhance elimination of poison.
5. Confirmation of agents involved.
6. Supportive care.

Stabilization:

1. Air way obstruction.
Bronchoconstriction and increase in respiratory secretion in OP poisoning.
Give atropine or use endotracheal tube.

2. Breathing
Ventilation , oxygenation, respiratory stimulants.
3. Circulation.

Fluid replacement , blood transfusion, antiarrythmic agents.

4. Depression and excitation.
In case of seizure give diazepam.
CNS depression give glucose, naloxon.

5. Fever or hypothermia.
Bathing with lukewarm water in case of fever.
Heating pads, hot water bottles, blankets.
6. Removal of source of toxicants.
7. Prevent further absorption .
8. Inactivate absorbed toxicant.
9. Elimination of absorbed toxicant.

Removal the source and prevent further absorption of toxicants

1. Animal removed from the source of poison.
2. Give food and water supply.
3. Elimination of poison from the skin.
4. Emesis (after 2hrs less effective).

- **Apomorphin for dogs**
- **Xylazine for cats.**
- **Contraindicated in the unconscious animals, severely depressed animals, petroleum intoxication, acids ingestion and alkalis.**

5.Gastric lavage (within 2 hrs following ingestion) by using stomach tube.
6.Gastrointestinal contaminant.
To prevent further absorption by formation of an insoluble precipitate or complex.
Sulfate (like lead or barium sulfate).
7. Cathartics hasten remove of the toxicants from GIT by increase mobility.
Na sulfate or Mg sulfate to evacuate the bowel.
Sorbitol given to improve the taste of charcoal.
Mineral oils , saline cathartics.

Enhance elimination of poison

Inactivation of toxicant by antidotal therapy

Antidotal therapy is accomplished by a number of mechanisms as:
1. Antidote may complex with toxicant rendering it inert.
e.g. Heavy metals chelated by EDTA and As (arsenic) which complexes with dimercaprol
2. Antidote accelerate conversion of toxicant to non toxic products . e.g. nitrite ion and thiosulfate ion complex with cyanide to form non toxic compound.

3. Antidote may block formation of toxic metabolite and form less toxic precursor.
e.g. ethyl alcohol compete with alcohol dehydrogenase and block formation of oxalic acid from ethylene glycol.
4. Antidote accelerates excretion of toxicant.
e.g. sulfate ion aid in rapid elimination of excess Cu in ruminants.
5. Antidote may compete with toxicant for essential receptors.
6. Antidote may block receptors responsible for toxic effects.

Diagnosis (confirmation) of toxicants

It involved:
1. Detailed case history.
2. Clinical signs and clinical pathology.
3. Post-mortem lesions.
4. Toxicant in the tissues (samples).
5. Animal bioassays.
6. Efficacy of treatment.

Sample collection:

1. No debris or contamination.
2. Package and label.
3. Proper storage.
The samples are blood refrigerate, fluid and tissues frozen, feed, stomach content, vomitus (dry or frozen).

Common specimens for analysis:
Water, urine, serum, whole blood, stomach contents, feces, bile, liver, kidney, brain, fat, plant material, soil, baits, grasses, corn, wheat.

General types of analysis:

1. Spot test and ELISA kits.
2. Screening :thin layer chromatography (TLC), gas chromatography (GC), high performance liquid chromatography(HPLC).
3. Quantitative: GC, HPLC, Atomic absorption spectrometry(AA).
4. Confirmation: GC-mass spectrometry (GC-MS

Elimination of toxicants

1. Increase glomerular filtration by give diuretics (diuresis)
e.g. mannitol or furosemide.
Alkaline urine enhances acidic toxicants excretion and vice viscera.
Ion trapping : changing urinary pH to enhance toxicants elimination.
2. Hemodialysis (artificial kidney)
Hemoperfusion, and hemofilitration (in human medicine)
e.g. Barbiturates, sedative, alcohol, antibiotics, metals.
In vet. Peritoneal dialysis (less effective).
3. Chelation
It used to deplete residues of heavy metals from tissues and bones e.g. penicillamine.

Supportive care:

1. Maintain renal function.
Saline , osmotic and forced diuretics.
2. Antibiotics
Treat secondary infections.
3. Diet.

Pharmaceutical poisoning

Acetaminophen:

Pain reliever (Tylenol, paracetol, panadol)

Phenacetin rapidly metabolized to acetaminophen .

Most intoxication occur after owners intentionally give the medication to cats or after accidental ingestion.

Mechanism of action:

Its rapidly absorbed from GIT and metabolized in liver.

Cats lack ability to glucuronidate acetaminophen more active metabolite (N-acetyl benzoquinone amine).

GSH depletion occurs and its synthesis inhibited.

Cats males more sensitive.

Death occurs due to exhaustion of hepatic and circulatory glutathione with result of methemoglobinemia ,hemolysis, Heinz body anemia ,Hburia and renal tubular necrosis in severe cases.

- **In dogs ---- hepatic necrosis .**
- **In cats ------ oxidative damage.**
- **Vomiting , depression, facial or paw edema, pale m.m., jaundice , dyspnea, cyanosis.**

Diagnosis:

1.Case history of exposure and clinical signs.

2.Pathology including Hienz bodies.

3.Hepatic and renal necrosis.

4.reduce PCV.

Treatment :

- **Within 24hrs.**
- **Less than 2hrs after exposure:**
- **Emetic, activated charcoal, saline cathartics.**
- **For sever affected animals:**
- **N-acetylcystein orally or I.V. in 5% dextrose.**
- **Mild case given I.V. dose.**

Alternative to N-acetylcystein:

- **Na-sulfate I.V. or 5-adenosyl methionine .**
- **Ascorbic acid used to correct metHbemia .**
- **Methylene blue I.V. In combination with N-acetylcystein beneficial in females.(not in males)**
- **Cimetidine to inhibit cytochrom P450 enzymes.**

Supportive therapy:

- **Blood transfusion , fluid, oxygen.**
- **Steroids may increase mortality.(contraindicated).**

Non-steroidal anti-inflammatory drugs

- **Salicylates(Aspirin), Pyrozolones(Phenylbutazone), Pyrolopyrones(Dipyrone), Oxicams(Piroxicam), Propionic acids(Ibuprofen), Indoleacetic acid (Indomethacin).**

Sources:

Accidental overdose or inappropriate therapy.

- **Prolong use higher than recommended.**
- **Wrong species or in combination.**

All animals are susceptible to poisoning e.g. dog, cat, and horse.

Mechanism of action:

1. Inhibition of cyclooxygenase and PG synthesis.
2. Inhibit platelet aggregation and promote bleeding (gastric).
3. Gastric irritation and ulceration.
4. Acidosis and CNS depression.

Clinical signs

- **GIT:**
- **Anorexia, bleeding vomiting ,bloody diarrhea and dehydration.**
- **Renal signs:**
- **Oliguria, Azotemia.**
- **Hematologic signs:**
- **Blood dyscrasis , abnormal platelet aggregation and bleeding, anemia, Heinz bodies in cats.**

Others:

- **Increase respiratory rate and alkalosis followed by acidosis which leads to depression.**
- **Cerebral and pulmonary edema.**
- **Hypernatremia, Hypokalemia, Seizures, Coma and death.**

- **Ibuprofen and naproxen: Nephrotoxic with GI signs.**
- **Acetylsalicylic acid : Teratogenic ,GI signs and haemostatic effects.**
- **Indomethacin: rare.**
- **Meclofenamic acid: GI ulceration and hemorrhage.**
- **Phenylbutazone: Acidosis, acute hypotension, blood dyscrasis.**

Dipyrone: Agranulocytosis and leucopenia.

Lesions:

1. Gastric ulceration and hemorrhage.
2. Increase clotting time and reduce platelet aggregation.
3. Renal and hepatic function change.
4. Blood chemistry: increase creatinine and BUN.
5. Urinary lesion: Hematuria, pyuria, proteinuria and casts.

Diagnosis:

1. Case history and clinical signs.
2. Lesions.
3. Tissue level of NSAIDs in blood, urine and tissue level

Treatment:

1. Emesis or lavage.(1st 8 hrs) with activated charcoal.
2. Na-bicarbonate.
3. Replaced fluid.
4. Correct acidosis and alkalinize urine.
5. Ventilation.
6. Peritoneal dialysis.
7. Vitamin K.
8. Diazepam.
9. Antacids (sucralfate) misoprosol or omeprazole .
10. Vassopressors.

Avoid nephrotoxic antibiotics (Gentamicin).

References:
Veterinary Toxicology, Reddy ,Evans and Casteel, 2011.
Clinical veterinary toxicology, Plumlee , 2004.