

UNIT-5

Principles of Toxicology

Toxicology is basically the study of poison on living organisms. OR,

Toxicology is the study of the adverse effects of xenobiotics on living organisms.

→ Toxicology encompasses the understanding of mechanisms by which toxins interact with biological systems, leading to toxicity.

→ Toxicology helps us understand the various aspects including the absorption, distribution, metabolism and excretion of toxic substances in the body.

→ Toxicology plays a crucial role in assessing the safety of pharmaceuticals, environmental pollutants, food additives and other chemicals.

Toxicity studies are divided into :

1) Acute Toxicity

Such studies aim to determine the adverse effects of a substance within a relatively brief period, usually 24 hrs. to 14 days.

They provide information on the substances toxicity at high doses and help establish initial safety guidelines.

2) Sub-Acute Toxicity

Sub-acute toxicity studies involve repeated exposure to a substance over several weeks to a few months, typically ranging from 28-90 days. These studies assess the effects of prolonged exposure on various organs and systems.

3) Chronic Toxicity

Chronic toxicity studies assess the adverse effects of long term exposure to a substance over a significant portion of an organism's lifespan, often lasting for several months to years.

Examples of chronic toxicity :

- 1) Long-term ethanol ingestion in alcoholics result in liver cirrhosis.
- 2) Several years of lead exposure in workmen causes kidney disease.

4) Genotoxicity

Genotoxicity is the ability of a substance to cause damage to genetic material (DNA) within cells.

Genotoxins can be defined as mutagens that cause genotoxicity resulting in damage of chromosomal material leading to mutation.

Depending upon the effect of genotoxins, they can be of following category:

- 1) Cancer causing agents or carcinogens
- 2) Birth defect causing agents (teratogens)
- 3) Mutation causing agents (mutagens)

MOA of genotoxicity :- Genotoxins damage genetic material in cells through exchanges with the DNA

sequence and structure.

An example of genotoxin is Pyrolozidine Alkaloids.

5) Carcinogenicity

Carcinogenicity refers to the ability of a substance or agent to cause cancer. This can include chemicals, radiation, biological agents or even certain behaviors or lifestyles.

Carcinogens are chemicals that induces or increases the chances of cancer.

International Agency for Research on Cancer (IARC), a part of WHO classify carcinogens as follows:

1) Group-1 :- Carcinogenic to Humans (full evidences).

2) Group-2A :- Probably Carcinogenic to Humans.

This group comprises agents for which there is limited evidence of carcinogenicity in humans but sufficient evidence from animal studies or other sources which says that they are likely to cause cancer in humans.

Examples - formaldehyde, glyphosate, etc.

3) Group-2B :- Possibly Carcinogenic to Humans.

This group includes agents for which there is limited evidence of carcinogenicity in humans but less consistent evidence from animal studies.

Examples- coffee, diesel exhaust, etc.

4) Group-3 :- Not classifiable as carcinogenic to humans.

This category includes agents for which the available evidence is inadequate to determine whether an agent is carcinogenic or not in humans.

Examples- talc and certain food additives.

5) Group-4 :- Probably not carcinogenic to humans.

This category includes agents for which there is strong evidence indicating that they do not cause cancer in humans.

Examples- caprolactam and saccharin.

Mechanism of Carcinogens

Carcinogens can initiate cancer by inducing mutations in critical genes, such as tumor suppressor genes, leading to uncontrolled cell growth.

6) Teratogenicity

Teratogenicity refers to the ability of certain substances or environmental factors to disrupt the normal development of a fetus during pregnancy which can lead to birth defects or developmental abnormalities.

These substances, called as teratogens, can include drugs, chemicals, infectious agents or physical agents like radiation.

Types of Teratogens

1) Chemical Teratogens :- Drugs, industrial chemicals, pesticides, pollutants.

2) Physical Teratogens :- Radiation, heat, etc.

3) Biological Teratogens :- Viruses, bacteria, and parasites can cause birth defects if the mother has an infection during pregnancy.

Mechanism of Teratogenicity

Teratogens may interfere with the normal process of cell division and differentiation, leading to structural abnormalities.

7) Mutagenicity

Mutagenicity refers to the ability of substances to induce changes called mutations, in the genetic material (DNA) of an organism. These mutations can lead to alterations in the sequence of DNA, which can have various harmful effects.

Mutations are of two types:

1) Spontaneous mutations :- These mutations occur at the time of normal growth and development.

2) Induced Mutations :- These mutations occur as a result of environmental mutagens, like radiation, chemicals, etc.

Mechanisms of Mutagenicity

1) Mutagens can cause DNA damage, such as chemical modifications or strand breaks, which lead to errors during replication or repair.

2) Some mutagens interfere with DNA replication by inserting themselves into DNA sequences, disrupting normal gene function.

3) Mutagens may also activate oncogenes, promoting cancerous growth.

Examples of different mutagens include:

- 1) Acidine Orange
- 2) Nitrogen Mustard
- 3) Cosmic rays
- 4) Hydrogen and atomic bombs

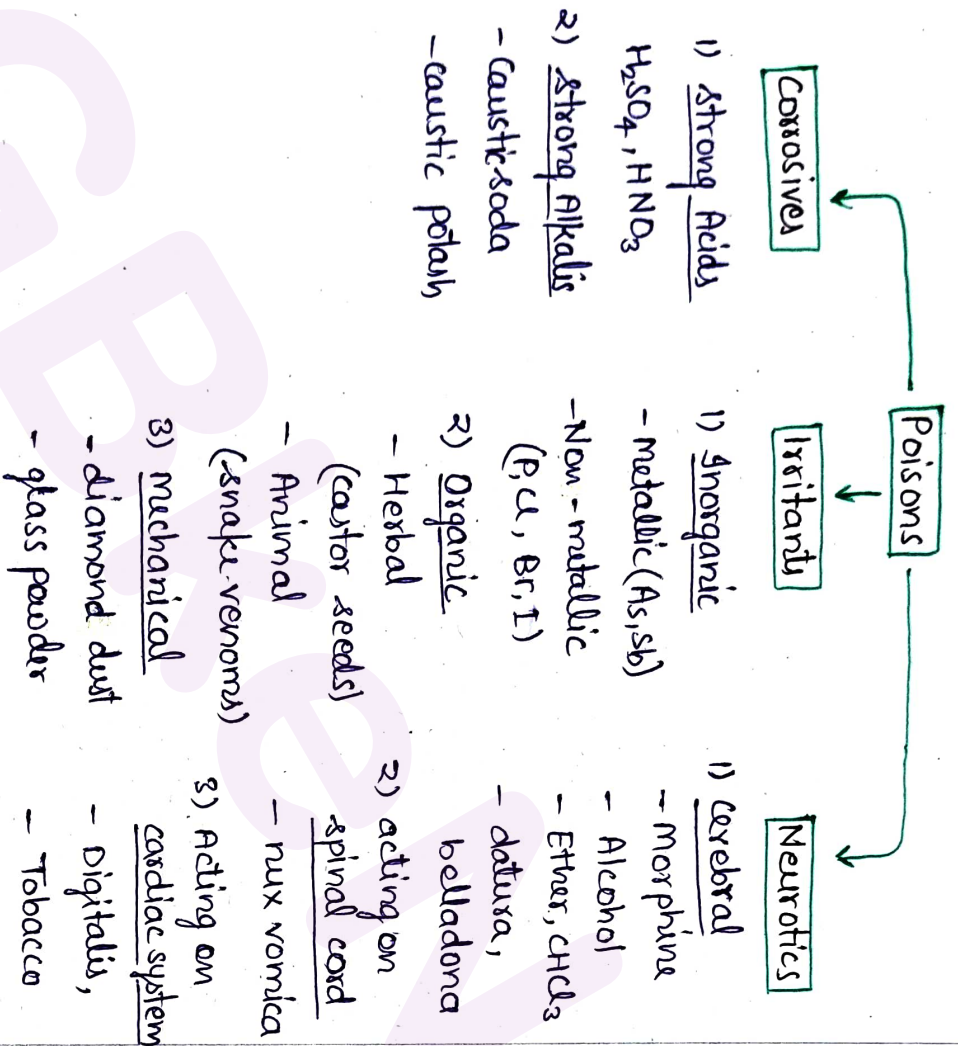
General Principles of Treatment of Poisoning

Poison → It refers to any substance ingested into the body by any route and has the potential to interfere with the life processes of body organs of an organism.

A poison can impair the normal physiology of body by killing or injuring through its chemical actions.

→ A poison can be a solid, a gas or a liquid.

Also, any of the essential nutrients, medicines or drugs can act as poisons under some specific conditions.

ClassificationTreatment of Poisoning

- 1) Poison identification :- Depending upon the symptoms and other factors, the poison must be identified.

2) Maintaining clear passages :- Debris must be removed, e.g., mucus, vomitus and the secretions, from the endo-tracheal region.

3) Ensure proper ventilation :- Proper tidal volume must be kept up by mechanical ventilators. Under-ventilation can cause hypoxemia and over-ventilation may lead to alkalosis and hypotension.

4) Fluid and electrolyte therapy :- Isotonic saline (0.9% w/v) or isotonic glucose (5% w/v) or plasma may be used. It is done to expand the circulating blood volume and restoration of cardiac output.

5) Prevention of further absorption of poison :-

(1) From the environment :- the patient should be removed from the toxic environment and contaminated clothing should also be removed and the skin should be cleansed.

(ii) From the gut :-

a) Oral adsorbents :- Activated charcoal (carbonix, medicals) reduces drug absorption.

b) Gastric lavage :- This involves removal of un-absorbed poison from the stomach.

The stomach contents pass out in 3-4 hours, thus a stomach wash should be done before this time interval.

c) Emetics :- 15 gm of sodium chloride is dissolved in a glass of water and given to make the patient vomit.

6) Specific Antidotes :- These should be given in case of any specific type of poisoning.

e.g. paracetamol poisoning should be treated with N-acetylcysteine (NAC).

7) Methods of poison elimination:

- i) Repeated dose of charcoal
- ii) Dialysis and Diuresis
- iii) Changing pH of urine

Barbiturate Poisoning

Barbiturate poisoning often results from an overdose of barbiturate drugs. Barbiturates are CNS depressants that are used as sedatives, hypnotics and anticonvulsants.

Symptoms of barbiturate poisoning

1) Central Nervous System Depression: Barbiturates depress the CNS activity leading to symptoms such as drowsiness, confusion, lethargy, shock, headache. In severe cases, coma may occur.

2) Respiratory Depression :- shallow breathing, respiratory arrest.

3) Hypotension :- Barbiturates can cause a drop in blood pressure, leading to symptoms like dizziness, fainting and shock.

4) Hypothermia :- lowers body temperature

5) Bradycardia :- Barbiturates may slow down the heart rate.

Management of Barbiturate Poisoning

1) Supportive Care:- Focusing on stabilizing the patient's vital signs and ensuring adequate oxygenation and ventilation.

2) Airway Management:- Maintaining patient's airway is crucial, especially in cases of respiratory depression or coma. Mechanical ventilation may be required.

3) Activated charcoal:- Activated charcoal may be administered to help absorb the barbiturate in the stomach and prevent further absorption into the bloodstream.

4) Enhanced Elimination:- In severe cases, techniques such as hemodialysis or hemoperfusion may be considered to enhance the elimination of barbiturates from the blood.

5) Monitoring:- Continuous monitoring of vital signs, including respiratory rate, heart rate, blood pressure and oxygen saturation, is essential.

6) Other Supportive Measures: Treatment may include the injection of intravenous fluids to maintain hydration and support blood pressure.

Morphine Poisoning

Morphine poisoning is characterized by the presence of symptoms resulting from the excessive presence of morphine in the body. Morphine is a CNS depressant and a potent opioid medication used primarily for pain relief, but its misuse or accidental ingestion in excessive amounts can lead to poisoning.

Clinical symptoms

1) Respiratory depression:- slow or shallow breathing or even complete stopping of breathing.

2) CNS depression:- drowsiness, confusion, sedation and loss of consciousness.

3) Hypotension :- Low blood pressure can lead to dizziness and fainting.

4) Bradycardia :- slowed heart rate may occur.

5) Constricted Pupils :- Morphine overdose often leads to pinpoint pupils.

6) GI symptoms :- nausea, vomiting, constipation.

Management of Morphine Poisoning

1) Airway management :- Ventilatory support is crucial in respiratory depression or arrest.

2) Naloxone Administration :- Naloxone is a medication that can rapidly reverse the effects of opioid overdose by blocking opioid receptors in the brain.

3) Monitoring :- continuous monitoring of vital signs is essential.

4) Gastric lavage and activated charcoal :- In some cases, gastric lavage (clearing out the contents of stomach) or administration of activated charcoal may be considered to reduce further absorption of morphine from GI tract.

Organophosphorus compound Poisoning

organophosphorus compounds (OPs) are chemicals that inhibit the activity of acetylcholinesterase, an enzyme essential for proper functioning of the nervous system.

OPs poisoning occurs when individuals are exposed to chemicals which contain OPs, which are commonly found in pesticides, insecticides. When exposed to these compounds, it leads to the accumulation of acetylcholine, resulting in overstimulation of cholinergic receptors throughout the body. This overstimulation causes a range of symptoms, collectively known as OPs poisoning.

Clinical symptoms

- 1) Excessive salivation
- 2) Lacrimation (tears)
- 3) Urination
- 4) Defecation
- 5) GI distress (diarrhea, abdominal cramps)

- 6) Bradycardia or tachycardia
- 7) Miosis (constricted pupils)
- 8) Muscle weakness or paralysis
- 9) Respiratory distress or failure
- 10) Seizures, coma.

Management

- 1) Decontamination :- Remove contaminated clothing and wash the skin with soap and water. If ingestion has occurred, it's crucial to prevent further absorption by administering activated charcoal.
- 2) Antidotes :- Administer antidotes such as atropine and pralidoxime (2-PAM).
- 3) Bronchial secretions are to be removed by suction.
- 4) Gastric lavage
- 5) Maintaining adequate respiration and airway functioning.

Lead Poisoning

Lead poisoning is typically defined as having a blood lead level greater than 5 micrograms per deciliter. Lower levels can cause toxicity in children. It occurs when lead builds up in the body, often over a period of months or years.

Clinical symptoms

In children, symptoms may include developmental delays, learning difficulties, irritability, loss of appetite, weight loss, abdominal pain, hearing loss and seizures.

In adults, symptoms may include high BP, joint and muscle pain, memory loss, mood disorders, abdominal pain, constipation and tingling.

Management

- 1) Removing the source of lead :- Removing lead-based paint from homes, replacing lead plumbing and avoiding products that may contain lead, such as certain toys, cosmetics and pottery.

2) Chelation Therapy :- In cases of severe

lead poisoning, chelation agents such as EDTA or DMSA are administered to help remove lead from the body.

3) Nutritional Support :- A diet rich in iron, calcium and vitamin C can reduce the absorption of lead in the body.

Mercury Poisoning

Mercury is also known as Para or quick silver.

Mercury poisoning, also known as mercurialism, occurs when mercury accumulates in the body overtime.

Mercury can exist in three forms :

- 1) Elemental form
- 2) Organic form
- 3) Inorganic form

each with different toxicological properties.

→ common sources of exposure include contaminated seafood, dental amalgam fillings, occupational exposure in industries such as mining.

Clinical Symptoms

1) Neurological symptoms :- tremors, irritability, anxiety, memory loss, difficulty concentrating, depression, insomnia and in severe cases, paralysis may occur.

2) GI symptoms :- nausea, vomiting, diarrhea, abdominal pain.

3) Respiratory symptoms :- coughing, chest tightness and shortness of breath.

4) Renal symptoms :- proteinuria (excessive protein in the urine), hematuria (blood in urine).

5) Other symptoms :- Other possible symptoms include, skin rashes, headaches, weakness, fatigue and anorexia.

Management

1) Removal of the source :- Identify and eliminate the sources of mercury exposure to prevent further toxicity.

- 2) Chelation Therapy :- It involves the administration of chelating agents, which bind to mercury and facilitate its excretion from the body.
- commonly used chelators include dimecaprol (BAL), DMSA (meso-2,3-dimercaptosuccinic acid) and DMPS (2,3-dimercapto-1-propane sulfonic acid).
- 3) Symptomatic treatment may be necessary to manage specific symptoms. For example, antiemetics can alleviate nausea and vomiting; while medications such as benzodiazepines or antidepressants may be given to manage neurological symptoms.
- 4) Regular monitoring of blood and urine mercury levels as well as renal function tests may be necessary.
- 5) Preventive measures such as proper ventilation in workplaces, appropriate disposal of mercury-containing products, etc. can help reduce the risk of mercury poisoning.

Arsenic Poisoning

Arsenic poisoning refers to the toxic effects caused by the ingestion, inhalation or absorption of arsenic compounds into the body. Arsenic is highly toxic and can be found in water, soil, air and food.

Arsenic poisoning occurs when someone is exposed to high levels of arsenic.

Clinical Symptoms

- 1) GI symptoms :- abdominal pain, nausea, vomiting, diarrhea, cramping.
- 2) Neurological symptoms :- headache, dizziness, weakness, and numbness.
- 3) Skin :- darkening of skin, thickening of skin, hair loss.
- 4) Respiratory symptoms :- coughing, irritation, shortness of breath, chest tightness.
- 5) Cardiovascular symptoms :- irregular heartbeat, hypertension, or even heart failure in severe cases.

Management

- 1) Immediate removal from exposure :- Suspected individual should be removed from the source of exposure to prevent further poisoning.
- 2) Supportive care :- This includes treating symptoms such as GI upset with antiemetics and intravenous fluids to maintain hydration.
- 3) Chelation Therapy :- Chelating agents such as BAL, DMSA or DMPS can help remove arsenic from the body by binding to it and facilitate its excretion.
- 4) Patients with arsenic poisoning should be closely monitored for any complications and follow-up care may be needed to assess their recovery and long-term health effects.

Chronopharmacology

Chronopharmacology is a specialised field within pharmacology that focuses on understanding how the timing of drug administration affects its pharmacological activity and interactions with the body's biological clock.

The concept of chronopharmacology comes from the fact that safety and efficacy of medications can vary depending upon the time of day they are administered. This variation arises from the body's internal biological clock, which governs daily rhythms in physiological functions such as sleep-wake cycles, hormone secretion, body temperature and metabolism.

Mechanism

- 1) Drug Absorption :- Biological rhythms impact GI motility and blood flow affecting drug absorption. This makes certain times more favourable for optimal absorption.

2) metabolism :- Administering drugs during peak metabolic activity can enhance efficacy or reduce toxicity.

3) Drug Distribution :- Circadian variations in blood flow and receptor sensitivity affect drug distribution and receptor binding, respectively.

Rhythm / circadian Rhythm

Rhythms refer to recurring, patterned sequences of events or activities that occur over a period of 24 hours.

Circadian rhythms enables the organisms to maintain and restrict their activities according to the day and night time.

Example- The circadian rhythm regulates the sleep-wake cycle, hormone secretion and metabolism, following a roughly 24-hour pattern.

Biological cycle

Biological cycles denote repetitive sequences of biological phenomena completing a full circle within a defined time frame, often characterized by distinct phases or stages.

Example- The menstrual cycle in females, typically completing in about 28 days, including phases such as menstruation, follicular, ovulation and luteal.

Biological clock and their significance leading to chronotherapy

Chronotherapy → It means the administration of medication or treatment in coordination with the body's circadian rhythms to maximise effectiveness and minimize side effects.

Biological clocks, also known as circadian rhythms are internal mechanisms that regulate internal various physiological processes in living organisms

over a roughly 24-hour cycle. These processes include sleep-wake cycles, hormone secretion, metabolism, body temperature regulation and other behavioral and physiological patterns.

Significance

- 1) Circadian rhythms regulate sleep patterns, influencing sleep quality and duration.
- 2) Biological clocks govern the timing of hormone release, affecting metabolism, mood and physiological functions.
- 3) Circadian rhythms regulate body temperature which impact metabolic processes and overall health.
- 4) Medications may be more effective or less toxic when administered at specific times of day.
- 5) Chronotherapy aims to minimize side effects by administering medications at times when the body is most receptive to treatment and least susceptible to adverse effects.

Rhythms Affecting our Body

- 1) Ultradian :- cycles shorter than a day.
e.g. msec.
- 2) Circadian :- lasting for about 24 hours.
e.g. sleep and wake cycles.
- 3) Infradian :- cycles longer than 24 hours.
e.g. menstrual cycle.
- 4) Seasonal :- Seasonal Affective Disorder (SAD) causing depression in people during the short days of winter.