PHARMACEUTICAL TOXICOLOGY

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Basic Definitions

TOXICOLOGY

> study of xenobiotics

> involves internal and external physiological exposure to toxins and their interactions with the body's components

> Almost any chemical has the potential for toxicity

> branch of Pharmacology that deals with the study of poison, mechanism of toxicity and its treatment.

POISON

> ***Corpus delecti***

> any agent which may cause serious body injury, disease or death when applied, introduced into or developed within the body.

Basic Definitions

AGENTS AND TOXINS

> Agents – compounds, chemicals or drugs

> Toxins – agents inducing undesirable effects.

INTOXICATION

> Toxicity associated with any chemical substance

POISONING

> a clinical toxicity secondary to ACCIDENTAL exposure

Overdose

> an INTENTIONAL exposure with the intent of causing self-injury or

Basic Definitions

RISK ASSESSMENT

> estimate of potential effects of poison to human health and environmental significance of various types of chemical exposure.

HAZARD

> likelihood that injury will occur in each situation or setting

RISK

> expected frequency of the occurrence of an undesirable effect arising from exposure to a chemical or physical agent

HISTORY

- Toxicology dates to the earliest humans
- Poisons played an important role in the history of humankind. In most cases, poisoning is caused by people's negative characteristics
- This may be a lack of information, ignorance, carelessness, untidiness, and, at worst, anger that may lead to cases of deliberate poisoning
- 50-400 A.D: Romans used poisons for executions and assassinations
- The philosopher Socrates was executed using Hemlock for teaching radical ideas to youths.
- 1200 A.D.: Spanish rabbi Maimonides writes a first-aid book for poisonings: **Poisons and their Antidotes**

HISTORY

- Swiss Physician Paracelsus (1493-1541) is credited with being ''the father of modern toxicology''
- Set the basics of pharmacology, toxicology and therapeutics
- Investigated dose-response relationship
- 'All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy''.

HISTORY

- Italian Physician Ramazzini (1713): Father of Occupational Medicine
- Outlined health hazards of the dusts, fumes, or gases that such workers inhaled
- His research led to the current diagnosis: allergen-induced asthma (horse riders and bakers)
- Pneumoconiosis: a group of dust-related chronic diseases (miners, farmers, glass cutters)

HISTORY

- 20th century
- Rachel Carson alarmed the public about the dangers of pesticides in the environment

AREAS OF TOXICOLOGY

CLINICAL TOXICOLOGY

> specific discipline of the broader filed of toxicology concerned with the TOXIC EFFECTS of agents whose intent is to treat, ameliorate, modify or prevent disease states, or the effect of drugs which, at one time, were intended to be used as such

> involves not only the toxic effects of therapeutic agents but also those chemicals whose intentions is not therapeutic.

- ✓Environmental components
- ✓Drug use because of societal behavior
- ✓Chemical by-products of industrial development
- ✓Essential components of urban, suburban or agricultural technologies.

MECHANISTIC TOXICOLOGY

> identification of the cause of toxicity of a chemical at the cellular or organismal level.

>MOA/ mechanism of action

> eg: blindness associated to methanol intoxication

EXPERIMENTAL TOXICOLOGY

> Investigation of the toxic effects of chemicals in the biological system measures laboratory parameters (LD 50, LC50, and TLV)

REGULATORY TOXICOLOGY

> administrative dogma associated with the availability of potential toxins encountered in the society

> defines, directs and dictates the rate at which an individual may encounter a synthetic or naturally occurring toxin and establishes guidelines for its maintenance in the environment or within the therapeutic market.

DESCRIPTIVE TOXICOLOGY

> toxicity testing – safety evaluation and regulatory requirements

> subjective attempt at explaining the toxic agents and their applications

- ✓metals toxicology
- ✓Clinical
- ✓Genetic
- ✓Occupational
- ✓In-vitro
- ✓Analytical, cellular, molecular, and developmental
- ✓Immunotoxicology
- ✓neurotoxicology

ENVIROMENTAL TOXICOLOGY

> deals with the potentially deleterious impact of chemical, present as pollutants of the environment to living organisms

FORENSIC TOXICOLOGY

> medico-legal aspects if the harmful effect of chemicals on humans and animals.

TYPES OF TOXICOLOGISTS

1. Forensic Toxicologists
2. Clinical Toxicologists -identification, diagnosis and treatment of a condition, pathology or disease resulting from environmental, therapeutic or illicit exposure to chemical or drugs.
3. Research Toxicologists – examine the broad issues in toxicology in the laboratory
4. Regulatory Toxicologists – sanction, approve, and monitor the use of chemicals by enforcing rules and guidelines

POISON

> deleterious effect
> physical injuries
> death

TOXIN –natural source
TOXICANTS – man made/ artificial source

COMMON MAJOR PATHOPHYSIOLOGIC MECHANISMS	
CNS stimulation	Causes nerve excitability → Seizures → Brain damage
CNS depression	Loss of airway protective reflexes and respiratory drive → Respiratory depression
Parasympathomimetic effect (**DUMBELS**)	**D**iarrhea **U**rination **M**iosis, **M**uscle fasciculations **B**ronchoconstriction, **B**radycardia **E**mesis **L**acrimation **S**alivation, **S**weating
Sympathomimetic effects (**MATHS**)	**M**ydriasis **A**gitation **T**achycardia **H**ypertension **S**eizure, **S**weating
Cardiovascular effects	Heart: Cardiac Arrhythmias Vasculature: • Vasodilation → hypotension • Vasoconstriction → hypertension
Respiratory effects	Aspiration → Bronchospasm
Cellular hypoxia	Interference with O_2 transport and utilization
Musculoskeletal effects	Muscle breakdown and myoglobinuria → Renal failure, lactic acidosis, hyperkalemia

POISON

Sola dosis faict venenum – " the dose makes the poison"

Side effects/ adverse effects

> aka. Deleterious/ toxic effects

1. Hypersensitivity
2. Idiosyncrasy
3. Tolerance/ desensitization
4. Teratogenicity

US FDA PREGNANCY RISK CLASSIFICATION

Category	Animal studies	Human studies
A	Safe	Safe
B	Safe	None
	NOT SAFE	Safe
C	NOT SAFE	None
	None	None
D	NOT SAFE: benefits outweigh risk	
X	Contraindicated in pregnancy = Teratogenic effects	

TERATOGENS

Teratogens	Presentation
Thalidomide	Amelia/ Phocomelia
Warfarin	Hypoplastic nose
Tetracycline	Tooth discoloration
Lithium	Ebstein's anomaly
ACE inhibitors	Renal dysgenesis
Methimazole	Aplasia cutis
Carbamazepine, Valproic acid	Neural tube defects (spina bifida)
Diethylstilbestrol (DES)	Clear cell adenocarcinoma of the vagina/ cervix
Phenytoin	Fetal hydantoin syndrome
Ethanol	Fetal alcohol syndrome • Facial anomalies • Growth retardation • Neuro-developmental defects

EFFECTS OF POISON

Immediate vs. Delayed

Immediate	Delayed
• Seen after single administration	• Seen after a lapse of time

Reversible vs. Irreversible

Reversible	Irreversible
• Reversed by administration of the antidote	• Permanent damage • Carcinogenic and teratogenic effects

Local vs. Remote vs. Systemic

Local	Remote	Systemic
• Same route of administration and site of action	• Different route of administration and site of action	• Causes widespread derangement
Example: Phenol, caustic, corrosives → skin burn	Example: Paraquat ingestion → pulmonary fibrosis	Example: Metabolic acidosis due to MUDPHILES

MUDPHILES
Methanol
Uremia
Diabetic ketoacidosis
Paraldehyde
Isoniazid, **I**ron
Lactic acidosis
Ethylene glycol
Salicylates

FACTORS AFFECTING POISONING

Poison-Related Factors:

Route of Administration

> Injected poisons are more toxic compared to poisons swallowed.

Concentration

> As the dose is increased, the probability of toxicity increases

FACTORS AFFECTING POISONING

Solubility

> Poisons that are highly lipid-soluble are absorbed via the skin

> Poisons with high water solubility may be absorbed faster orally than those with poor water solubility.

FACTORS AFFECTING POISONING

Patient-related Factors:

Age

> The liver of a pediatric patient is not yet fully developed, which may cause the accumulation of drugs even when given at normal doses.

> Geriatric patients have slower metabolizing rates compared to adults aged 20-40

FACTORS AFFECTING POISONING

Habit

> for chain smokers and alcoholics

Tolerance

> e.g. nicotine

Idiosyncrasy

> Genetic defects may lead to toxicity

Route of Administration

1. Ingestion – accidental and suicidal poisoning
2. Inhalational – occupational exposure
3. Dermal – occupational exposure
4. Parenteral – greatest effect and most rapid response

Frequency

1. Acute
    - -single administration
    - -time: < 24 hours
    - - acute exposure by inhalation: 4 hours
2. Subacute
    - - repeated exposure
    - - < 1 month
3. Sub-chronic
    - - repeated exposure
    - - 1-3 months
4. Chronic
    - - repeated exposure
    - - 3 months

EVIDENCE OF POISONING

Circumstantial

> deduced from various events or facts

> not strong evidence

Post-mortem

> gathered after an autopsy is performed
(examination of tissues, organs, and body fluids after death)

EVIDENCE OF POISONING

Experimental

> Administering the suspected substance to a living animal and noting the effect or symptom

Chemical

> Detection of suspected substance via analysis of samples of body fluids collected

Symptomatic

> contributed by signs and symptoms

CLASSIFICATION OF TOXIC AGENTS

1. Classification by Target Organ (Systemic Toxicity)
    1. Hepatotoxins
    2. Nephrotoxins
    3. Neurotoxins
    4. Immunotoxins
    5. Pulmonotoxins
    6. Hematotoxins

CLASSIFICATION OF TOXIC AGENTS

2. Classification by Mechanism of Action
    1. Enzyme inhibitors
    2. Carcinogens
    3. Mutagens
    4. Teratogens
    5. Asphyxiants

CLASSIFICATION OF TOXIC AGENTS

3. Classification by source or Origin
    1. Biotoxins
    2. Synthetic/chemical
    3. Environmental/mineral

CLASSIFICATION OF TOXIC AGENTS

4. Classification by Physical State
    1. Gases and vapors
    2. Solids/dusts
    3. Liquids
    4. Radiation

CLASSIFICATION OF TOXIC AGENTS

5. Classification by Use or Function
    1. Pesticides
    2. Industrial solvents
    3. Household chemicals
    4. Therapeutic drugs
    5. Chemical warfare agents

CLASSIFICATION OF TOXIC AGENTS

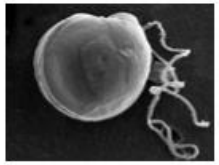
Zootoxins

Tetrodotoxin

Cantharidin

Clupeotoxin

Scromboid



Ciguatoxin

Zootoxins

Latrotoxin

5-hydroxytryptamine

Apitoxin

Hyaluronidase

CLASSIFICATION OF TOXIC AGENTS

Phytotoxins

Poison	Source/s
Arecoline	Betel nut
Brucine, strychnine	Nux vomica
Picrotoxin	Fish berries Equimolar mixture of two compounds, picrotoxinin and picrotin
Myristicin	Nutmeg
Cicutoxin	water hemlock Cicuta douglasii
Colchicines	Autumn crocus
Convallarin	Lily of the valley *Convallaria majalis*
Coniine	Poison hemlock *Conium maculatum*
Phenanthridine	Daffodil, jonquil *Narcissus pseudonarcissus*
Podophyllotoxin	American mandrake, May apple *Podophyllum peltatum*

CLASSIFICATION OF TOXIC AGENTS

Mushroom Toxins

Group	Toxin	Source/s
I	Amanitotoxins, cyclopeptides	Hepatotoxins
IA	Orellanine, orelline	Nephrotoxins
II	Muscimo, Iboteric acid	Hallucinogens, Anticholinergic signs & symptoms
III	Gyrometrin	Hepatotoxin
IV	Muscarine	Cholinergic overstimulation
V	Coprine	Disulfiram reaction
VI	Psilocin, psilocybin	Hallucinogens

Microbial Toxins

Poison	Source/s
Saxitoxin	Dinoflagellates
Aflatoxin	Aspergillus flavus
Ptomaine	Bacterial decay
Tyrotoxicon	Bacterial decay
Ergot	Claviceps purpurea
Exotoxins	Mostly from Gram(+)
Botulinum toxin	C. botulinum
Tetanospasmin	C. tetani
ALPHA toxin	C. perfringens