Principles of Toxicology

1. Introduction to Toxicology

- **Definition**: Toxicology is the study of the adverse effects of chemical, physical, or biological agents on living organisms and the environment, including their prevention and treatment.
- **Scope**: Includes identification, mechanism, dose-response relationships, and management of toxic effects.
- **Types of Toxicants**:
    - Chemical: Drugs, pesticides, heavy metals.
    - Physical: Radiation, heat.
    - Biological: Toxins from plants, animals, or microbes.
- **Key Terminologies**:
    - **Toxin**: Naturally occurring poisonous substance (e.g., snake venom).
    - **Toxicant**: Synthetic or man-made poisonous substance (e.g., pesticides).
    - **LD50**: Dose lethal to 50% of the test population (measure of acute toxicity).
    - **ED50**: Dose effective in 50% of the population (therapeutic effect).
    - **Therapeutic Index**: Ratio of LD50 to ED50 (indicates drug safety).
    - **Xenobiotic**: Foreign chemical substance not naturally produced in the body.

2. Classification of Toxicants

- **Based on Source**:
    - Natural: Snake venom, botulinum toxin.
    - Synthetic: Drugs, industrial chemicals (e.g., benzene).
    - Environmental: Air pollutants, heavy metals (e.g., lead, mercury).
- **Based on Target Organ**:
    - Hepatotoxins: Affect liver (e.g., paracetamol overdose).
    - Nephrotoxins: Affect kidneys (e.g., aminoglycosides).
    - Neurotoxins: Affect nervous system (e.g., organophosphates).
    - Cardiotoxins: Affect heart (e.g., digitalis).
- **Based on Effect**:
    - Acute: Immediate effects after single exposure (e.g., cyanide poisoning).
    - Chronic: Effects after prolonged exposure (e.g., lead toxicity).
    - Subacute/Subchronic: Intermediate effects.
- **Based on Chemical Nature**:
    - Heavy metals: Lead, mercury, arsenic.
    - Organic compounds: Alcohols, hydrocarbons.
    - Gases: Carbon monoxide, hydrogen sulfide.

3. Principles of Toxicity

- **Dose-Response Relationship**:
    - Toxicity depends on dose, frequency, and duration of exposure.
    - **Threshold Dose**: Minimum dose required to produce a toxic effect.

    - **Linear vs. Non-linear**: Some toxins show a linear dose-response, others have a threshold.
- **Routes of Exposure**:
    - Oral (e.g., drug overdose).
    - Inhalation (e.g., carbon monoxide).
    - Dermal (e.g., pesticide absorption).
    - Parenteral (e.g., intravenous toxins).
- **Factors Affecting Toxicity**:
    - **Host Factors**: Age, sex, genetic makeup, health status.
    - **Chemical Factors**: Solubility, stability, chemical structure.
    - **Environmental Factors**: Temperature, co-exposure to other substances.
- **Mechanisms of Toxicity**:
    - **Direct Tissue Damage**: Corrosives (e.g., acids, alkalis).
    - **Enzyme Inhibition**: Organophosphates inhibit acetylcholinesterase.
    - **Receptor Interaction**: Toxins mimic or block endogenous ligands.
    - **Oxidative Stress**: Free radical generation (e.g., paracetamol overdose).
    - **Metabolic Activation**: Conversion of non-toxic to toxic metabolites (e.g., cytochrome P450 activation of carbon tetrachloride).

4. Types of Toxicities

- **Acute Toxicity**:
    - Occurs within hours or days of exposure.
    - Examples: Cyanide poisoning, organophosphate poisoning.
    - Symptoms: Rapid onset (e.g., convulsions, respiratory failure).
- **Chronic Toxicity**:
    - Results from repeated or prolonged exposure.
    - Examples: Lead poisoning, arsenic-induced cancers.
    - Symptoms: Delayed onset, cumulative damage (e.g., neuropathy, organ failure).
- **Subacute/Subchronic Toxicity**:
    - Intermediate duration (weeks to months).
    - Example: Repeated low-dose exposure to heavy metals.
- **Developmental Toxicity**:
    - Affects fetus (e.g., thalidomide causing phocomelia).
- **Carcinogenic Toxicity**:
    - Leads to cancer (e.g., benzene causing leukemia).
- **Mutagenic Toxicity**:
    - Causes genetic mutations (e.g., radiation exposure).
- **Teratogenic Toxicity**:
    - Causes congenital malformations (e.g., alcohol causing fetal alcohol syndrome).

5. Management of Poisoning

- **General Principles**:
    - **Stabilization**: Ensure airway, breathing, circulation (ABCs).
    - **Assessment**: Identify toxin, route, dose, and time of exposure.
    - **Decontamination**: Reduce further absorption.

        - **Skin/Eye**: Wash with water or saline.
        - **Gastrointestinal**:
            - **Gastric Lavage**: Rarely used; within 1-2 hours of ingestion.
            - **Activated Charcoal**: Adsorbs toxins (effective within 1 hour).
            - **Whole Bowel Irrigation**: For sustained-release drugs or heavy metals.
    - **Elimination Enhancement**:
        - Forced diuresis (e.g., for barbiturates).
        - Hemodialysis (e.g., for methanol, ethylene glycol).
        - Alkalinization of urine (e.g., for salicylates).
    - **Antidote Administration**: Specific antidotes (see below).
    - **Supportive Care**: Manage symptoms (e.g., anticonvulsants for seizures).
- **Prevention of Absorption**:
    - Activated charcoal: 1 g/kg body weight, most effective within 1 hour.
    - Cathartics: Magnesium sulfate to hasten elimination (used cautiously).
- **Monitoring**: Vital signs, ECG, renal/liver function tests.

6. Specific Antidotes

- **Antidote**: A substance that counteracts a specific poison by neutralizing it or reversing its effects.
- **Common Antidotes**:
    1. **N-acetylcysteine (NAC)**:
        - **Poison**: Paracetamol (acetaminophen) overdose.
        - **Mechanism**: Replenishes glutathione, detoxifies NAPQI (toxic metabolite).
        - **Dose**: Oral (140 mg/kg loading, then 70 mg/kg every 4 hours for 17 doses) or IV.
    2. **Atropine and Pralidoxime (2-PAM)**:
        - **Poison**: Organophosphate poisoning.
        - **Mechanism**: Atropine blocks muscarinic effects; 2-PAM regenerates acetylcholinesterase.
        - **Dose**: Atropine 1-2 mg IV every 5-10 min; 2-PAM 1-2 g IV.
    3. **Flumazenil**:
        - **Poison**: Benzodiazepine overdose.
        - **Mechanism**: Competitive antagonist at GABA receptor.
        - **Dose**: 0.2 mg IV over 30 seconds, repeated as needed.
    4. **Naloxone**:
        - **Poison**: Opioid overdose.
        - **Mechanism**: Opioid receptor antagonist.
        - **Dose**: 0.4-2 mg IV, repeat every 2-3 minutes.
    5. **Deferoxamine**:
        - **Poison**: Iron overdose.
        - **Mechanism**: Chelates free iron.
        - **Dose**: 15 mg/kg/hr IV infusion.
    6. **Dimercaprol (BAL)**:
        - **Poison**: Heavy metals (arsenic, mercury, lead).
        - **Mechanism**: Chelates metals to form excretable complexes.
        - **Dose**: 3-5 mg/kg IM every 4-6 hours.
    7. **Sodium Bicarbonate**:
        - **Poison**: Salicylates, tricyclic antidepressants.

        - **Mechanism**: Alkalinizes urine, enhances excretion, stabilizes cardiac membranes.
        - **Dose**: 1-2 mEq/kg IV bolus.
    8. **Ethanol or Fomepizole**:
        - **Poison**: Methanol or ethylene glycol.
        - **Mechanism**: Inhibits alcohol dehydrogenase, prevents toxic metabolite formation.
        - **Dose**: Fomepizole 15 mg/kg IV loading dose; ethanol 10 mL/kg IV.
    9. **Vitamin K**:
        - **Poison**: Warfarin or rodenticide poisoning.
        - **Mechanism**: Restores clotting factor synthesis.
        - **Dose**: 5-10 mg IV or oral.
    10. **Glucagon**:
        - **Poison**: Beta-blocker overdose.
        - **Mechanism**: Increases cardiac contractility via cAMP.
        - **Dose**: 3-10 mg IV bolus.

7. Specific Toxicities and Management

- **Paracetamol Overdose**:
    - **Mechanism**: Excess NAPQI depletes glutathione, causes hepatotoxicity.
    - **Symptoms**: Nausea, vomiting, jaundice, liver failure (after 24-48 hours).
    - **Management**: N-acetylcysteine, monitor liver function tests, use Rumack-Matthew nomogram.
- **Organophosphate Poisoning**:
    - **Mechanism**: Inhibits acetylcholinesterase, causing cholinergic crisis.
    - **Symptoms**: SLUDGE (Salivation, Lacrimation, Urination, Defecation, GI distress, Emesis), miosis, bradycardia.
    - **Management**: Atropine, pralidoxime, decontamination, supportive care.
- **Heavy Metal Poisoning**:
    - **Lead**: Neurotoxicity, anemia, colic. **Antidote**: Dimercaprol, EDTA.
    - **Mercury**: Nephrotoxicity, tremors. **Antidote**: Dimercaprol.
    - **Arsenic**: GI distress, neuropathy. **Antidote**: Dimercaprol or succimer.
- **Carbon Monoxide Poisoning**:
    - **Mechanism**: Binds hemoglobin, reduces oxygen delivery.
    - **Symptoms**: Headache, confusion, cherry-red skin, coma.
    - **Management**: 100% oxygen, hyperbaric oxygen therapy.
- **Opioid Overdose**:
    - **Symptoms**: Respiratory depression, pinpoint pupils, coma.
    - **Management**: Naloxone, ventilatory support.

8. Toxicokinetics and Toxicodynamics

- **Toxicokinetics**: How the body handles toxins (absorption, distribution, metabolism, excretion).
    - **Absorption**: Depends on route (e.g., oral slower than inhalation).
    - **Metabolism**: Phase I (oxidation, reduction) and Phase II (conjugation) reactions.
    - **Excretion**: Kidneys (primary), bile, lungs.

- **Toxicodynamics**: Biochemical and physiological effects of toxins.
    - Example: Cyanide inhibits cytochrome oxidase, halting cellular respiration.

9. Toxicological Testing

- **Acute Toxicity Testing**: Determines LD50, single-dose effects.
- **Chronic Toxicity Testing**: Assesses long-term exposure effects (e.g., carcinogenicity).
- **In Vitro Tests**: Cell-based assays for cytotoxicity.
- **In Vivo Tests**: Animal studies for systemic effects.

10. Prevention of Poisoning

- Safe storage of chemicals and drugs.
- Child-proof packaging.
- Public education on poison control.
- Proper labeling of toxic substances.
- Emergency contact: Poison control centers (e.g., in India: AIIMS Poison Information Centre).
