Pharmacology-2
Toxicology
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Toxicology

- Humans live in a chemical environment and inhale, ingest, or absorb from the skin many of these chemicals.

Toxicology:

- Toxicology is concerned with the deleterious effects of these chemical agents on all living systems.

Clinical toxicology:

- Clinical toxicology focuses on diseases that are caused by or are uniquely associated with toxic substances.

- **Occupational toxicology** deals with the chemicals found in the workplace.
- The major emphasis of occupational toxicology is to identify the agents of concern, define the conditions leading to their safe use, and prevent absorption of harmful amounts.

- **Ecotoxicology** is concerned with the toxic effects of chemical and physical agents on *populations* and *communities of living organisms* within defined ecosystems; it includes the transfer pathways of those agents and their interactions with the environment.
- Traditional toxicology is concerned with toxic effects on individual organisms; ecotoxicology is concerned with the impact on populations of living organisms or on ecosystems.

Toxicants	substances that produce adverse biological effects of any nature may be chemical or physical in nature effects may be of various types *(acute, chronic, etc.)*
Toxins	specific proteins produced by living organisms *(mushroom toxin or tetanus toxin)* most exhibit immediate effects
Poisons	toxicants that cause immediate death or illness when experienced in very small amounts

Organic toxins	substances that were originally derived from living organisms *(thus named organic)* contain carbon and often are large molecules can be synthesized *(that is man-made)* as well as be obtained from natural sources
Inorganic toxins	specific chemicals that are not derived from living organisms *(minerals)* generally small molecules consisting of only a few atoms *(such as nitrogen dioxide)*

Environmental toxicology:

- Environmental toxicology deals with the potentially deleterious impact of chemicals, present as pollutants of the environment, on living organisms.
- The term *environment* includes all the surroundings of an individual organism, but particularly the air, soil, and water.

- Air pollution is a product of industrialization, technologic development, and increased urbanization.
- Humans may also be exposed to chemicals used in the agricultural environment as pesticides or in food processing that may persist as residues or ingredients in food products.

- **Hazard** is *the ability of a chemical agent to cause injury in a given situation or setting;* the conditions of use and exposure are primary considerations.
- **Risk** is defined as *the expected frequency of the occurrence of an undesirable effect* arising from exposure to a chemical or physical agent.

Routes of Exposure:

- The route of entry for chemicals into the body differs in different exposure situations.
- In the industrial setting, inhalation is the major route of entry.
- The transdermal route is also quite important, but oral ingestion is a relatively minor route.

Duration of Exposure:

- Toxic reactions may differ qualitatively depending on the duration of the exposure.
- A single exposure—or multiple exposures occurring over 1 or 2 days—represents **acute exposure.**
- Multiple exposures continuing over a longer period of time represent a **chronic exposure.**

AIR POLLUTANTS:

- Five major substances account for about 98% of air pollution:

1. Carbon monoxide (about 52%).
2. Sulfur oxides (about 14%).
3. Hydrocarbons (about 14%).
4. Nitrogen oxides (about 14%).
5. Particulate matter (about 4%).

- The sources of these chemicals include transportation, industry, generation of electric power, space heating, and refuse disposal.

Carbon Monoxide

- Carbon monoxide (CO) is a colorless, tasteless, odorless, and nonirritating gas, a byproduct of incomplete combustion

Mechanism of Action

- CO combines reversibly with the oxygen-binding sites of hemoglobin and has an affinity for hemoglobin that is about 220 times that of oxygen.
- The product formed, carboxyhemoglobin, cannot transport oxygen, reducing the transfer of oxygen to tissues.
- The brain and the heart are the organs most affected.

Clinical Effects

- The principal signs of CO intoxication are those of hypoxia and progress in the following sequence:
- (1) Psychomotor impairment
- (2) Headache and tightness in the temporal area

- (3) confusion and loss of visual acuity
- (4) tachycardia, tachypnea, syncope, and coma
- (5) deep coma, convulsions, shock, and respiratory failure.

Treatment

- In cases of acute intoxication, removal of the individual from the exposure source and maintenance of respiration is essential, followed by administration of oxygen (the specific antagonist to CO).

Sulfur Dioxide

- Sulfur dioxide (SO_2) is a colorless, irritant gas generated primarily by the combustion of sulfur-containing fossil fuels.

Mechanism of Action

- On contact with moist membranes, SO_2 forms sulfurous acid, which is responsible for its severe irritant effects on the eyes, mucous membranes, and skin.

- It is estimated that approximately 90% of inhaled SO_2 is absorbed in the upper respiratory tract, the site of its principal effect.
- The inhalation of SO_2 causes bronchial constriction; parasympathetic reflexes and altered smooth muscle tone appear to be involved in this reaction.

Clinical Effects & Treatment

- The signs and symptoms of intoxication include irritation of the eyes, nose, and throat and reflex bronchoconstriction.
- If severe exposure has occurred, delayed onset pulmonary edema may be observed.
- Treatment is not specific for SO_2 but depends on therapeutic maneuvers utilized in the treatment of irritation of the respiratory tract.

Nitrogen Oxides

- Nitrogen dioxide (NO_2) is a brownish irritant gas sometimes associated with fires.

Mechanism of Action

- NO_2 is a deep lung irritant capable of producing pulmonary edema.
- The type I cells of the alveoli appear to be the cells chiefly affected on acute exposure.

Clinical Effects & Treatment

- The signs and symptoms of acute exposure to NO_2 include irritation of the eyes and nose, cough, mucoid or frothy sputum production, dyspnea, and chest pain.
- Pulmonary edema may appear within 1–2 hours

- There is no specific treatment for acute intoxication by NO_2; therapeutic measures for the management of deep lung irritation and noncardiogenic pulmonary edema are employed.
- These measures include maintenance of gas exchange with adequate oxygenation and alveolar ventilation.
- Drug therapy may include bronchodilators, sedatives, and antibiotics.

Ozone

- Ozone (O_3) is a bluish irritant gas that occurs normally in the earth's atmosphere, where it is an important absorbent of ultraviolet light.
- In the workplace, it can occur around high-voltage electrical equipment and around ozone-producing devices used for air and water purification.
- It is also an important oxidant found in polluted urban air.

Clinical Effects & Treatment

- O_3 is an irritant of mucous membranes.
- Mild exposure produces upper respiratory tract irritation.
- Severe exposure can cause deep lung irritation, with pulmonary edema when inhaled at sufficient concentrations.
- Long-term exposure in animals results in morphologic and functional pulmonary changes e.g. Chronic bronchitis, bronchiolitis, fibrosis.

- There is no specific treatment for acute O_3 intoxication.
- Management depends on therapeutic measures utilized for deep lung irritation and noncardiogenic pulmonary edema.

Chemical Forms of Drugs That Produce Toxicity:

- The "parent" drug administered to the patient often is the chemical form producing the desired therapeutic effect; the parent drug also may produce the toxic effects of drug.
- However, both therapeutic and toxic effects also can be due to metabolites of the drug produced by enzymes, light, or reactive oxygen species.
- In considering the toxicity of drugs and chemicals, it is important to understand their metabolism, activation, or decomposition.

Types of Toxic Reactions:

- Toxic effects of drugs may be classified as pharmacological, pathological, or genotoxic (alterations of DNA).
- An example of a pharmacological toxicity is excessive depression of the central nervous system (CNS) by barbiturates.
- An example of a pathological effect, hepatic injury produced by acetaminophen.

- An example of a genotoxic effect, a neoplasm produced by a nitrogen mustard.
- If the concentration of chemical in the tissues does not exceed a critical level, the effects usually will be reversible.
- The pharmacological effects usually disappear when the concentration of drug or chemical in the tissues is decreased by biotransformation or excretion from the body.

- Pathological and genotoxic effects may be repaired.
- If these effects are severe, death may ensue within a short time; if more subtle damage to DNA is not repaired, cancer may appear in a few months or years in laboratory animals or in a decade or more in humans.

Local toxicity:

- Local toxicity occurs at the site of first contact between the biological system and the toxicant.
- Local effects can be caused by ingestion of caustic substances or inhalation of irritant materials.

Systemic toxicity:

- Systemic toxicity requires absorption and distribution of the toxicant; most substances, with the exception of highly reactive chemical species, produce systemic toxic effects.

Reversible and Irreversible Toxic Effects:

- If a chemical produces injury to a tissue, the capacity of the tissue to regenerate or recover largely will determine the reversibility of the effect.
- Injuries to a tissue such as liver, which has a high capacity to regenerate, usually are reversible.
- Injury to the CNS is largely irreversible because the highly differentiated neurons of the brain have a more limited capacity to divide and regenerate.

Toxicokinetics & Toxicodynamics:

- The term **toxicokinetics** denotes the absorption, distribution, excretion, and metabolism of toxins, toxic doses of therapeutic agents, and their metabolites.
- The term **toxicodynamics** is used to denote the injurious effects of these substances on vital function.

Prevention and treatment of poisoning:

Initial Management Of The Poisoned Patient:

- toxic agents can be divided into two classes:
- a- Those for which a specific treatment or antidote exists.
- b-those for which there is no specific treatment.

- For the vast majority of drugs and other chemicals, there is no specific treatment; symptomatic medical care that supports vital functions is the only strategy.
- The adage, **"Treat the patient, not the poison,"** remains the most basic and important principle of clinical toxicology.

- Maintenance of respiration and circulation takes precedence.
- The basis ("**ABCDs**") of poisoning treatment:
- 1- The **airway** should be cleared of vomitus or any other obstruction and an oral airway or endotracheal tube inserted if needed.
- 2- **Breathing** should be assessed by observation and oximetry and, if in doubt, by measuring arterial blood gases.
- Patients with respiratory insufficiency should be intubated and mechanically ventilated.

- 3- The **circulation** should be assessed by continuous monitoring of pulse rate, blood pressure, urinary output, and evaluation of peripheral perfusion.
- 4- Every patient with altered mental status should receive a challenge with concentrated **dextrose**, unless a rapid bedside blood glucose test demonstrates that the patient is not hypoglycemic.

Decontamination:

- Decontamination procedures should be undertaken simultaneously with initial stabilization, diagnostic assessment, and laboratory evaluation.
- Decontamination involves removing toxins from the skin or gastrointestinal tract.

A. SKIN:

- Contaminated clothing should be completely removed and double-bagged to prevent illness in health care providers and for possible laboratory analysis.
- Wash contaminated skin with soap and water.

B. GASTROINTESTINAL TRACT:

- For most ingestions, clinical toxicologists recommend simple administration of activated charcoal to bind ingested poisons in the gut before they can be absorbed.
- In unusual circumstances, induced emesis or gastric lavage may also be used.

C. Inhalation and dermal exposure to poisons:

- When a poison has been inhaled, the first priority is to remove the patient from the source of exposure.
- Similarly, if the skin has had contact with a poison, it should be washed thoroughly with water.
- Contaminated clothing should be removed.
- Initial treatment of all types of chemical injuries to the eye must be rapid; thorough irrigation of the eye with water for 15 minutes should be performed immediately.

Enhanced Elimination of the Poison:

- 1- Biotransformation.
- 2- Biliary Excretion.
- 3- Urinary Excretion: forced diuresis and urinary PH manipulation.
- 4- Dialysis: Hemodialysis and peritoneal dialysis.
- 5- Antagonism or Chemical Inactivation of an Absorbed Poison.

Antidote	Poison(s)	Comments
Acetylcysteine (Mucomyst)	Acetaminophen	Best results if given within 8–10 hours of overdose. Follow liver function tests and acetaminophen blood levels. Acetylcysteine is given orally in the USA. Intravenous acetylcysteine has been used successfully in Europe and is under trial in the USA.
Atropine	Anticholinesterases: organophosphates, carbamates	A test dose of 1–2 mg (for children, 0.05 mg/kg) is given IV and repeated until symptoms of atropinism appear (tachycardia, dilated pupils, ileus). Dose may be repeated every 10–15 minutes, with decrease of secretions as therapeutic end point.
Bicarbonate, sodium	Membrane-depressant cardiotoxic drugs (tricyclic antidepressants, quinidine, etc)	1–2 mEq/kg IV bolus usually reverses cardiotoxic effects (wide QRS, hypotension). Give cautiously in heart failure (avoid sodium overload).
Calcium	Fluoride; calcium channel blockers	Large doses may be needed in severe calcium channel blocker overdose. Start with 15 mg/kg IV.
Deferoxamine	Iron salts	If poisoning is severe, give 15 mg/kg/h IV. Urine may become pink. 100 mg of deferoxamine binds 8.5 mg of iron.
Digoxin antibodies	Digoxin and related cardiac glycosides	One vial binds 0.5 mg digoxin; indications include serious arrhythmias, hyperkalemia.
Esmolol	Theophylline, caffeine, metaproterenol	Short-acting β-blocker reverses β_1-induced tachycardia and (possibly) β_2-induced vasodilation. Infuse 25–50 μg/kg/min IV.
Ethanol	Methanol, ethylene glycol	Ethanol therapy can be started before laboratory diagnosis is confirmed. A loading dose is calculated so as to give a blood level of at least 100 mg/dL (42 g/70 kg in adults).
Flumazenil	Benzodiazepines	Adult dose is 0.2 mg IV, repeated as necessary to a maximum of 3 mg. *Do not give to patients with seizures, benzodiazepine dependence, or tricyclic overdose.*
Fomepizole	Methanol, ethylene glycol	More convenient and easier to use than ethanol. Loading dose 15 mg/kg; repeat every 12 hours.

Glucagon	ß-blockers	5–10 mg IV bolus may reverse hypotension and bradycardia that was resistant to ß-agonist drugs. May cause vomiting.
Naloxone	Narcotic drugs, other opioid derivatives	A specific antagonist of opioids; 1–2 mg initially by IV, IM, or subcutaneous injection. Larger doses may be needed to reverse the effects of overdose with propoxyphene, codeine, or fentanyl derivatives. Duration of action (2–3 hours) may be significantly shorter than that of the opioid being antagonized.
Oxygen	Carbon monoxide	Give 100% by high-flow nonrebreathing mask; use of hyperbaric chamber is controversial.
Physostigmine	Suggested for antimuscarinic anticholinergic agents; not for tricyclic antidepressants	Adult dose is 0.5–1 mg IV slowly. The effects are transient (30–60 minutes), and the lowest effective dose may be repeated when symptoms return. May cause bradycardia, increased bronchial secretions, seizures. Have atropine ready to reverse excess effects. *Do not use for tricyclic antidepressant overdose.*
Pralidoxime (2-PAM)	Organophosphate cholinesterase inhibitors	Adult dose is 1 g IV, which should be repeated every 3–4 hours as needed or preferably as a constant infusion of 250–400 mg/h. Pediatric dose is approximately 250 mg. No proved benefit in carbamate poisoning.

COMMON TOXIC SYNDROMES

1. ACETAMINOPHEN

- Acetaminophen is one of the drugs most commonly involved in suicide attempts and accidental poisonings, both as the sole agent and in combination with other drugs.
- Acute ingestion of more than 150–200 mg/kg (children) or 7 g total (adults) is considered potentially toxic.

- A highly toxic metabolite is produced in the liver .
- Initially, the patient is asymptomatic or has mild gastrointestinal upset (nausea, vomiting).
- After 24–36 hours, evidence of liver injury appears, with elevated aminotransferase levels and hypoprothrombinemia.
- In severe cases, fulminant liver failure occurs, leading to hepatic encephalopathy and death.

- Renal failure may also occur.
- The severity of poisoning is estimated from a serum acetaminophen concentration measurement.
- If the level is greater than 150–200 mg/L approximately 4 hours after ingestion, the patient is at risk for liver injury.

- The antidote acetylcysteine acts as a glutathione substitute, binding the toxic metabolite as it is being produced.
- It is most effective when given early and should be started within 8–10 hours if possible.
- A liver transplant may be required for patients with fulminant hepatic failure.

2. ASPIRIN (SALICYLATE)

- Salicylate poisoning is a much less common cause of childhood poisoning deaths since the introduction of child-resistant containers and the reduced use of children's aspirin.
- It still accounts for numerous suicidal and accidental poisonings.
- Acute ingestion of more than 200 mg/kg is likely to produce intoxication.

- Poisoning can also result from chronic overmedication; this occurs most commonly in elderly patients using salicylates for chronic pain who become confused about their dosing.
- Poisoning causes uncoupling of oxidative phosphorylation and disruption of normal cellular metabolism.

- The first sign of salicylate toxicity is often hyperventilation and respiratory alkalosis due to medullary stimulation.
- Metabolic acidosis follows, and an increased anion gap results from accumulation of lactate as well as excretion of bicarbonate by the kidney to compensate for respiratory alkalosis.
- Body temperature may be elevated due to uncoupling of oxidative phosphorylation.

- Severe hyperthermia may occur in serious cases.
- Vomiting and hyperpnea as well as hyperthermia contribute to fluid loss and dehydration.
- With very severe poisoning, profound metabolic acidosis, seizures, coma, pulmonary edema, and cardiovascular collapse may occur.

- After massive aspirin ingestions aggressive gut decontamination is advisable, including gastric lavage, repeated doses of activated charcoal, and consideration of whole bowel irrigation.
- Intravenous fluids are used to replace fluid losses caused by tachypnea, vomiting, and fever.

- For moderate intoxications, intravenous sodium bicarbonate is given to alkalinize the urine and promote salicylate excretion by trapping the salicylate in its ionized, polar form.
- For severe poisoning (eg, patients with severe acidosis, coma, and serum salicylate level > 100 mg/dL), emergency hemodialysis is performed to remove the salicylate more quickly and restore acid-base balance and fluid status.

3. DIGOXIN

- Digitalis and other cardiac glycosides are found in many plants and in the skin of some toads.
- Toxicity may occur as a result of acute overdose or from accumulation of digoxin in a patient with renal insufficiency or one taking a drug that interferes with digoxin elimination.

- Patients receiving long-term digoxin treatment are often also taking diuretics, which can lead to electrolyte depletion (especially potassium).
- Vomiting is common in patients with digitalis overdose.
- Hyperkalemia may be caused by acute digitalis overdose or severe poisoning, while hypokalemia may be present in patients as a result of long-term diuretic treatment.

- (Digitalis does not cause hypokalemia.)
- A variety of cardiac rhythm disturbances may occur, including sinus bradycardia, AV block, atrial tachycardia with block, accelerated junctional rhythm, premature ventricular beats, bidirectional ventricular tachycardia, and other ventricular arrhythmias.

- General supportive care should be provided.
- Atropine is often effective for bradycardia or AV block.
- The use of digoxin antibodies has revolutionized the treatment of digoxin toxicity.

- Symptoms usually improve within 30–60 minutes after antibody administration.
- Digoxin antibodies may also be tried in cases of poisoning by other cardiac glycosides (eg, digitoxin, oleander), although larger doses may be needed due to incomplete cross-reactivity.