Menoufia University, Faculty of Pharmacy
Course Specifications

Program on which the course is given	**BSc in pharmaceutical sciences**
Major or minor element of program	**Major**
Department offering the course	**Pharmacology & toxicology**
Department supervising the course	
Academic Year / Level	**Third year, first semester**
Date of specification approval	**9/2019**

Basic Information

Title: Toxicology	**Code: PO 904**
Credit Hours :3	**Lecture: 2**
Tutorial:	**Practical: 2**
Total contact hours:4	

Contents

Week	Topic	Total contact hours	Lecture	practical
1	Spectrum of toxicity	**3**	**2**	**1**
2	Toxicity testing	**3**	**2**	**1**
3	Management of poisoned patients	**3**	**2**	**1**
4	Carbon monoxide and cyanide poisoning	**3**	**2**	**1**
5	Heavy metals toxicity	**3**	**2**	**1**
6	Food & animal poisoning	**3**	**2**	**1**
7	**Mid-term exam**			**1**
8	Insecticides	**3**	**2**	**1**
9	Digitalis toxicity	**3**	**2**	**1**
10	Teratogenicity	**3**	**2**	**1**
11	Salicylate toxicity	**3**	**2**	**1**
12	Paracetamol toxicity	**3**	**2**	**1**
13	Alcohol toxicity	**3**	**2**	**1**
14	Corrosives poisoning	**3**	**2**	Practical exam
15	Addiction and drug abuse	**3**	**2**	Practical exam

Teaching and learning methods

a. Lectures	**(√)**
b. Practical training / laboratory	**(√)**
c. Seminar / Workshop	**(√)**
d. Class Activity	**(√)**

Student assessment methods

Written mid-term exam	**To assess**	**The ability of students to follow-up The course subjects.**
Practical exam	**To assess**	**The gained experience in laboratory methods and techniques.**
Oral exam	**To assess**	**The ability of students in expressing and presenting their knowledge clearly and in systematic approach.**
Written final exam	**To assess**	**The overall outcomes.**

Assessment schedule

Assessment 1	**Mid-term exam**	**Week**	**7**
Assessment 2	**Practical exam**	**Week**	**14,15**
Assessment 3	**Final exam**	**Week**	**16,17**
Assessment 4	**Oral**	**Week**	**16,17**

Weighting or assessments

Mid-Term Examination	**10**	**%**
Final-Term Examination	**50**	**%**
Oral Examination	**20**	**%**
Practical Examination	**15**	**%**
Semester Work	**5**	**%**
Other types of assessment		**%**
Total	**100**	**%**

7. Facilities required for teaching and learning

-Class rooms.
-Laboratory facilities. –Library.
- Projectors (Overhead, video projector)

-Computers. –Internet.

Course coordinator:

Prof. Ahmed Mansour, ph.D.
Dr. Shady N. Allam, ph.D.
Dr. Marwa M. Mafouz, ph.D.

Date: 7 / 2 /2020

GENERAL TOXICOLOGY

Toxicology is the study of the adverse effects of chemicals on living organisms. A toxicologist is trained to examine the nature of those effects (including their cellular, biochemical and molecular mechanisms of action) and assess the probability of their occurrence. The variety of potential adverse effects and the diversity of chemicals in the environment make toxicology a very broad science. Therefore, toxicologists often specialize in one area of toxicology.

1. Classification of toxic agents:

Toxic agents are classified in terms of their target organs (liver, kidney), use (pesticide, solvent), source (animal and plant toxins) and effects (cancer, mutation, liver injury).

Toxic agents may also be classified in terms of their physical state (gas, dust, liquid), their chemical stability or reactivity (explosive, flammable, oxidizer), general chemical structure (aromatic amine, halogenated hydrocarbon) or poisoning potential (extremely toxic, very toxic, slightly toxic).

2. Poisoning episodes:

Poisoning episodes may be classified into four types:

Accidental poisoning:

This is most frequently encountered in children between the ages of 1 and 5 years and is the usual cause of poisoning in this age group.

Suicidal poisoning:

This is the commonest form of poisoning in adults and accounts for at least 95% of all poisoning admission to hospital. The peak age incidence for self-poisoning is between the ages of 20-35 years, but it is not uncommon

before the age of 15 years. Self-poisoning should be suspected in any episodes occurring over the age of 8 years.

Homicidal poisoning:

Acute poisoning as a method of homicide is very uncommon. Sporadic cases occur but in most the poisoning is subacute or chronic as with antimony, arsenic and thallium.

Non-accidental poisoning:

Non-accidental poisoning is the term given to the deliberate administration of a poison to a child by one of its parents and may be regarded as an extension of battered child syndrome.

3. Prevention of poisoning:

Prevention of poisoning requires adequate knowledge of the hazardous properties of substances by users. When prescribing drugs, always be alert to their toxic potentialities so that the first signs will be recognized and proper action taken.

Household poisoning:

- All containers should have safety closures. Medicines, insecticides and rodenticides should be stored in locked cabinets.
- Dye, polishes, kerosene and other household chemicals should never be left on a low shelf or on the floor.
- Dangerous solutions should never be left in drinking glasses.
- Parents should be educated to the dangers present in medicines and household chemicals.
- Parents must begin to teach their children at an early age the danger of touching, eating or playing with medicines, pesticides, household chemicals or plants.

Agricultural poisons:

- Insecticides, rodenticides and fungicides must be stored in well-marked containers with safety closures, preferably under lock and key. Use masks and exhaust ventilation during dry mixing.
- Wear protective clothing, goggles and oil resistant neoprene gloves when prolonged handling of poisons in petroleum oils or other organic solvents is necessary. Protective clothing should be removed and exposed skin washed thoroughly before eating.

Industrial chemicals:

- Dust-forming operations must be conducted in closed systems with local exhaust ventilation.
- Hoods for local exhaust ventilation should enclose the process as completely as possible to prevent dispersion of contaminants.
- Less toxic substances should be substituted wherever possible. For example, toluene or xylene can be substituted for benzene in many operations.
- Workers should be trained to understand the hazards involved and to avoid exposure by proper use of safety equipment.
- Gloves, goggles and protective clothing should be used wherever necessary.
- Workers should be instructed to report for examination at the first evidence of illness or injury.

Suicidal poisoning:

- The physician should avoid prescribing sedatives, hypnotics or tranquilizers for depressed or possibly suicidal persons, since they are responsible for more than 20% of suicidal deaths.

- Persons who have made unsuccessful attempts at suicide should have adequate follow-up psychiatric therapy.

4. Factors modifying the action of poisons:

A- Factors related to the toxicant:

i. Form and innate chemical activity:

For example, the toxicity of mercury vapor differs greatly from methyl mercury. Others slowly interfere only with a cell's function, for example, hydrogen cyanide binds to cytochrome oxidase resulting in cellular hypoxia and rapid death. Nicotine binds to chloinergic receptors in the CNS altering nerve conduction and inducing gradual onset of paralysis.

ii. Dosage:

For example, acute poisoning of ethyl alcohol produces CNS depression; however, chronic ethanolism leads to liver cirrhosis.

iii. Exposure route:

Some chemicals may be highly toxic by one route but not by others. For example, ingested chemicals, when absorbed from the intestine, distribute first to the liver and may be immediately detoxified. Inhaled toxicants immediately enter the general blood circulation and can distribute throughout the body prior to being detoxified by the liver.

iv. Absorption:

For example, ethanol is readily absorbed from the gastrointesitnal tract but poorly absorbed through the skin. Organic mercury is readily absorbed from the gastrointestinal tract; inorganic lead sulphate is not.

v. Distribution:

If a toxicant is lipid soluble it readily penetrates cell membranes.

vi. Metabolism:

Metabolism is a major factor in determining toxicity. The products of metabolism are known as metabolites. There are two types of metabolism, *detoxification* and *bioactivation.*

vii. Excretion:

The site and rate of excretion is another major factor affecting the toxicity of a xenobiotic. The kidney is the primary excretory organ, followed by the gastrointestinal tract and the lungs (for gases).

B- Factors related to the subject:

Age: Young people are more susceptible than older people.

Health: Healthy persons are more resistant to poisons than those in poor health.

Hypersensitivity: Natural or acquired hypersensitivity may increase the response to toxic agents.

Sex: Sex difference is sometimes observed e.g. women are more susceptible to some substances than men such as opiates and fatty soluble substances.

Race: Coloured races are generally less susceptible than the white races to poisons which are absorbed through the skin.

5. Interactions of Chemicals:

The effects of two chemicals given simultaneously may be:

- *Additive*, when the combined effect of two chemicals is equal to the sum of the effects of each agent given alone. For example, when tow organophosphate insecticides are given together, the cholinesterase inhibition is usually additive.
- *Synergistic*, when the combined effects of two chemicals are much greater than the sum of the effects of each agent given alone. For example, both carbon tetrachloride and ethanol are hepatotoxic

compounds, but together they produce much more liver injury than the mathematical sum of their individual effects on liver at a given dose would suggest.

- *Potentiative*, when one substance does not have a toxic effect on a certain organ or system but when added to another chemicals makes that chemical much more toxic. Isopropanol, for example, is not hepatotoxic but when it is administered in addition to carbon tetrachloride, the hepatotoxicity of carbon tetrachloride is much greater than that when it is given alone.
- *Antagonistic*, when two chemicals administered together interfere with each other's actions or one interferes with the action of the other.

MANAGEMENT OF POISONED PATIENTS

The first steps in treatment of a patient who has been poisoned are to evaluate the airway, breathing, and circulation, and to perform a complete history. Poisoning with drugs from certain classes, notably anticholinergics, cholinergics, opioids, and sympathomimetics, are associated with constellations of symptoms known as toxidromes. For example, anticholinergic poisoning is associated with delirium; hyperthermia; mydriasis; tachycardia; urinary retention; and warm and dry skin. For identification of electrolyte imbalances and/or impairment of liver and renal function, basic laboratory studies, such as a complete metabolic profile, are an important part of the workup for possible medication poisonings. Clinical presentation and history should help determine what other laboratory studies are indicated.

The next step in the management of a poisoned patient is to remove the unabsorbed poison from the gut and increase the excretion of absorbed poison from the body.

1- Gastric decontamination, through

- Emesis to evacuate the gastric contents
- Gastric lavage to also, evacuate the gastric content
- Activated charcoal to bind and adsorb the toxins inside the GIT
- Cathartics to enhance GIT elimination of toxins

A- Emesis:

It is induced by using of syrup of Ipecac, and this syrup has no benefit if used after several hours from exposure to toxins.

Contraindications to induced emesis include:

- ❖ Unconscious patients due to lack of a gag reflex, or are unable to protect their airway adequately are at risk of pulmonary aspiration.
- ❖ In case of ingestion of caustic agents, to avoid further damage during re-exposure of GIT to ingested toxins.
- ❖ Seizures make the patients at risk of aspiration of gastric contents.
- ❖ Ingestion of petroleum distillate due to avoid pneumonic aspiration.

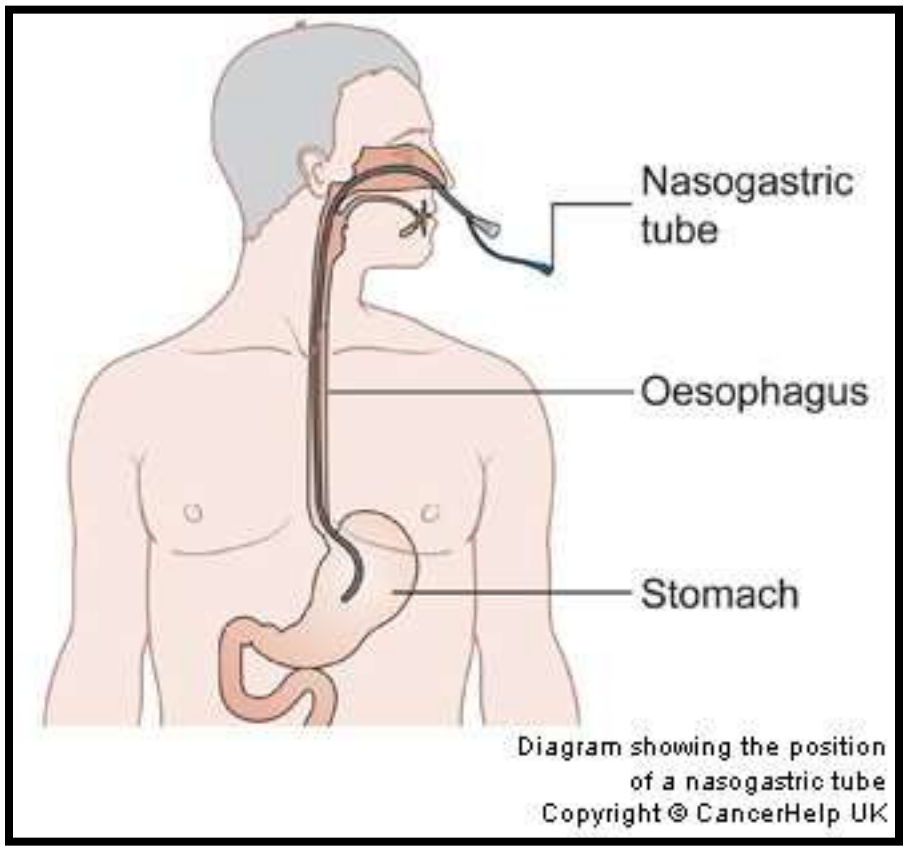
A dose of 30 ml is recommended for a patient over five years of age, followed by 240 ml to 360 ml of water. Patients less than five years should be given 15 ml, and those under one year should receive 10 ml, followed by 120-240 ml of water, a delay of 15 to 30 minutes between ipecac administration and initiation of vomiting is usual. If after 30 minutes emesis has not occurred, the dose may be repeated once.

B- Gastric lavage:

It can be performed in patients who are 1- do not vomit following ipecac or 2- in whom emesis is contraindicated.

Optimal return of gastric contents well be achieved by; placing the patient in the left lateral position when performing gastric lavage. Lavage is carried

out by alternating volumes of tap water and normal saline, following gastric lavage, activated charcoal and cathartics should be placed down the orogastric tube and left in the stomach.



C- Activated charcoal: is estimated to reduce absorption of poisonous substances up to 60%. It works by adsorbing chemicals, thus reducing their toxicity (poisonous nature), through the entire length of the stomach and small and large intestines (GI tract). Activated charcoal itself is a fine, black powder that is odorless, tasteless, and nontoxic. Because charcoal is not "digested," it stays inside the GI tract and eliminates the toxin when the person has a bowel movement. Activated charcoal will not be given to people with an obstruction of the intestines or if the person swallowed a corrosive agent, such as a strong acid or alkali.

D- Cathartics: such as sorbitol, magnesium citrate, magnesium sulfate, or sodium sulfate were previously used as a form of gastrointestinal decontamination following poisoning via ingestion. They are no longer routinely recommended for poisonings. High-dose cathartics may be an effective means of ridding the lower gastrointestinal tract of toxins; however, they carry a risk of electrolyte imbalances and dehydration.

2- Enhanced elimination, through

- ❖ Forced diuresis
- ❖ Hemodialysis
- ❖ Hemofiltration
- ❖ Hemoperfusion
- ❖ Peritoneal dialysis
- ❖ Blood transfusion

A- Forced alkaline or acid dieresis:

Most of the drugs are either weak acids or weak bases. When urine is made alkaline, elimination of acidic drugs in the urine is increased. The converse applies for alkaline drugs. This method is only of therapeutic

significance where the drug is excreted in active form in urine and where the pH of urine can be adjusted to levels above or below the pK value of the active form of drug. For acidic drugs, urine pH should be above the pK value of that drug, and converse for the basic drugs. It is because the ionization of acidic drug is increased in alkaline urine and ionized drugs cannot easily cross plasma membrane so cannot re-enter blood from kidney tubules. This method is ineffective for drugs which are strongly protein bound (e.g. tricyclic antidepressants) or which have a large apparent volume of distribution (e.g. paracetamol, tricyclic antidepressants).

Forced alkaline diuresis has been used to increase the excretion of acidic drugs like salicylates and phenobarbitone, while forced acid diuresis has been used to enhance the elimination of cocaine, amphetamine, quinine, quinidine, and strychnine when poisoning by these drugs has occurred. For forced alkaline diuresis, a diuretic like furosemide is given intravenously and sodium bicarbonate is added to the infusion fluid to make blood and, in turn, urine alkaline. Potassium replacement becomes of utmost importance in this setting because potassium is usually lost in urine. If blood levels of potassium are depleted below normal levels, then hypokalemia occurs, which promotes bicarbonate ion retention and prevents bicarbonate excretion, thus interfering with alkalinization of the urine.

For forced acid diuresis, ascorbic acid (vitamin C) is used. Ammonium chloride has also been used for forced acid diuresis but it is a toxic compound. Usually however, this technique only produces a slight increase in the renal clearance of the drug. Forced acid diuresis is rarely done in practice. Forced alkaline diuresis is also recommended for rhabdomyolysis.

A large number of drugs and chemicals may be removed by peritoneal or hemodialysis and charcoal or resin hemoperfusion.

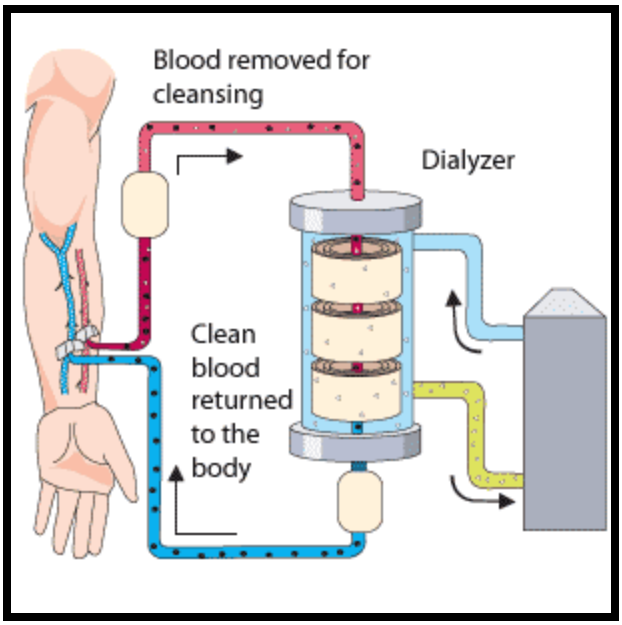
B- Hemodialysis:

The principle of hemodialysis is the same as other methods of dialysis; it involves diffusion of solutes across a semipermeable membrane. Hemodialysis utilizes counter current flow, where the dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit. Counter-current flow maintains the concentration gradient across the membrane at a maximum and increases the efficiency of the dialysis.

Fluid removal (ultrafiltration) is achieved by altering the hydrostatic pressure of the dialysate compartment, causing free water and some dissolved solutes to move across the membrane along a created pressure gradient.

The dialysis solution that is used may be a sterilized solution of mineral ions or comply with British Pharmacopoeia. Urea and other waste products, potassium, and phosphate diffuse into the dialysis solution. However, concentrations of sodium and chloride are similar to those of normal plasma to prevent loss. Sodium bicarbonate is added in a higher concentration than plasma to correct blood acidity. A small amount of glucose is also commonly used.

Note that this is a different process to the related technique of hemofiltration.

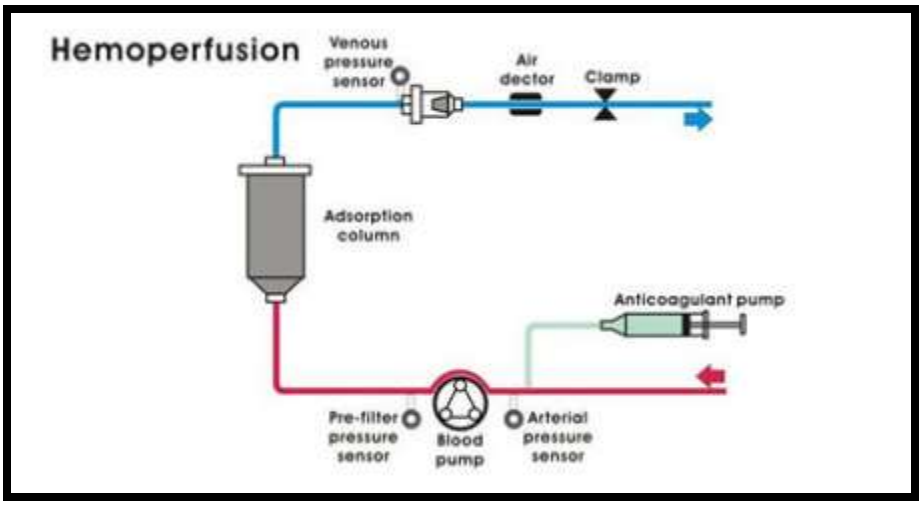


C- Hemofiltration:

As in dialysis, in hemofiltration one achieves movement of solutes across a semi-permeable membrane. However, solute movement with hemofiltration is governed by convection rather than by diffusion. With hemofiltration, dialysate is not used. Instead, a positive hydrostatic pressure drives water and solutes across the filter membrane from the blood compartment to the filtrate compartment, from which it is drained. Solutes, both small and large, get dragged through the membrane at a similar rate by the flow of water that has been engendered by the hydrostatic pressure. Thus convection overcomes the reduced removal rate of larger solutes (due to their slow speed of diffusion) seen in hemodialysis.

D- Hemoperfusion:

Hemoperfusion is a chemical process used to remove drugs or toxic substances from an individual's blood by passing it through a column of charcoal or other adsorbent material.



Hemoperfusion is often used as an effective method of drug removal from the blood stream in overdose cases.

- Blood is passed over an adsorbent substance in order to remove toxic substances in the blood
- Molecules or particles of a toxic substance are attracted to the surface of a solid absorbant material and adhere to it.
- Hemoperfusion may be referred to as an extracorporeal treatment due to the fact that the blood is processed outside the patient's body.

Sorbant or toxic chemical attractant materials:

- Resins
- Activated charcoal
- Activated carbon

Application:

- Removal of nephrotoxic drugs (kidney damaging drugs) or poisons from the blood in emergency situations (such as drug overdoses)
- Removal of waste products from the blood in patients with impaired kidney function or kidney disease

- Used to provide supportive treatment before and after transplantation for patients in liver failure, functions in blood metabolic waste product removal.

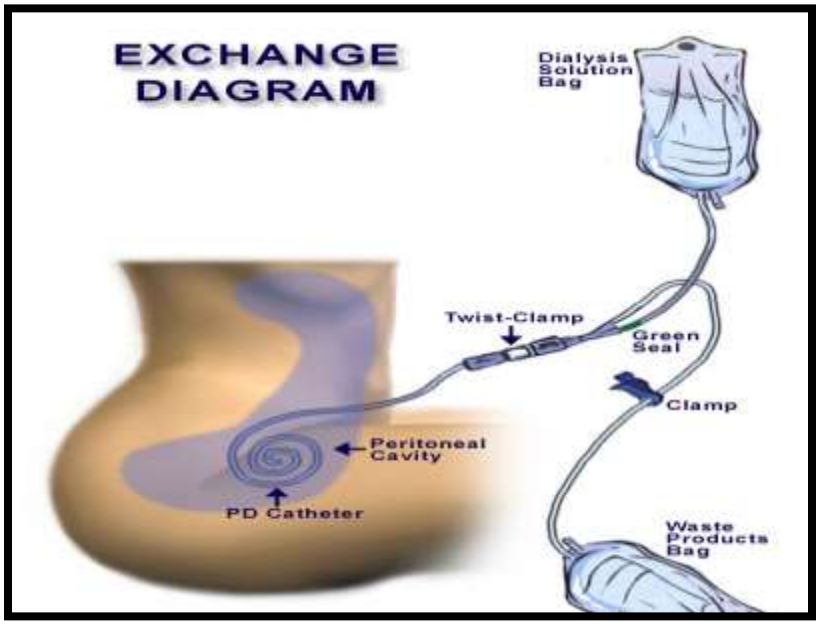
Process:

- A hemoperfusion system can be used with or without a hemodialysis machine.
- The patient is made comfortable
- Two catheters are placed in the arm, one in an artery and one in a nearby vein.
- The catheter in the artery is connected to tubing leading into the hemoperfusion system
- The catheter in the vein is connected to tubing leading from the system through a pressure monitor.
- The patient is given heparin (to thin the blood and prevent clotting) at the beginning of the procedure and at 15–20-minute intervals throughout the hemoperfusion.
- The patient's blood pressure is also taken regularly.
- A typical hemoperfusion treatment takes about three hours.
- Hemoperfusion functions to pump the blood drawn through the arterial catheter into a column or cartridge containing the sorbent material (to attract and bind the toxic substance).
- As the blood passes over the carbon or resin particles in the column, the toxic molecules or particles are drawn to the surfaces of the sorbent particles and trapped within the column.
- The blood flows out the other end of the column and is returned to the patient through the tubing attached to the venous catheter.

- Hemoperfusion is able to clear toxins from a larger volume of blood than hemodialysis or other filtration methods; it can process over 300 mL of blood per minute.

E- Peritoneal dialysis:

Peritoneal dialysis (PD) is a treatment for patients with severe chronic kidney disease. The process uses the patient's peritoneum in the abdomen as a membrane across which fluids and dissolved substances (electrolytes, urea, glucose, albumin and other small molecules) are exchanged from the blood. Fluid is introduced through a permanent tube in the abdomen and flushed out either every night while the patient sleeps (automatic peritoneal dialysis) or via regular exchanges throughout the day (continuous ambulatory peritoneal dialysis). PD is used as an alternative to hemodialysis though it is far less commonly used in many countries, such as the United States. It has comparable risks but is significantly less costly in most parts of the world, with the primary advantage being the ability to undertake treatment without visiting a medical facility. The primary complication of PD is infection due to the presence of a permanent tube in the abdomen.



DIGITALIS

Digitalis are commonly called **foxgloves**. The best-known species is the "Common Foxglove", *Digitalis purpurea*.

The term **digitalis** is also used for drug preparations that contain cardiac glycosides, particularly one called digoxin, that are extracted from various plants of this genus.

Medicinal use and mechanism of action:

It is used to increase cardiac contractility (it is a positive inotrope) and as an antiarrhythmic agent to control the heart rate, particularly in the irregular (and often fast) atrial fibrillation. A group of pharmacologically active compounds are extracted mostly from the leaves of the second year's growth, and in pure form are referred to by common chemical names such as ***digitoxin*** or ***digoxin***, or by brand names such as *Lanoxin*.

Digitalis works by inhibiting sodium-potassium ATPase. This results in an increased intracellular concentration of sodium ion and thus a decreased concentration gradient across the cell membrane. This increase in intracellular sodium activates a sodium/calcium exchange pump that brings calcium ions into the cell while extruding sodium in order to restore its gradient across the membrane. The increased cytosolic calcium ion concentration results in increased calcium ion storage in the sarcoplasmic reticulum. Upon action potential (cardiac contraction) more calcium is released from the sarcoplasmic reticulum and this gives a positive inotropic effect (higher contractility). Digitalis also has a vagal effect on the parasympathetic nervous system, and as such is used in reentrant cardiac arrhythmias and to slow the ventricular rate during atrial fibrillation.

Types of digoxin toxicity:

Digoxin toxicity is often divided into acute or chronic. The therapeutic level for digoxin is 0.8-2.0 ng/mL. Low serum potassium increases the risk of digoxin toxicity and cardiac dysrhythmias. The classic arrhythmia is a paroxysmal atrial tachycardia with block.

Digitalis toxicity can be caused by high levels of digitalis in the body, or a decreased tolerance to the drug. Patients with decreased tolerance may have "normal" digitalis levels in their blood.

People with heart failure who take digoxin are commonly given medications called diuretics, which remove excess fluid from the body. Many diuretics can cause potassium loss. Low levels of potassium in the body increase the risk of digitalis toxicity. Digitalis toxicity may also result in persons who take the drug and who have low levels of magnesium in the body.

Reduced kidney function will cause digitalis to build up in the body rather than be removed normally through urine. Therefore, any disorders that disrupt kidney functioning (including dehydration) make digitalis toxicity more likely.

Signs and symptoms of digoxin toxicity:

- Changes in heart rate and rhythm that were not present before: this manifests as irregular pulsation, tarchycardia (heart rate more than 100 beats per minute or bradycardia (heart rate less than 60 beats per minute).
- Visual disturbances (yellow or green halos around objects). Though this is not a very common symptom of digoxin toxicity but victims may experience blind spots in the visual field, blurred vision, changes in color perception, Halos or rings of light around objects, seeing lights or bright spots, blurred vision
- Hypersalivation: there is increased salivation,

- Fatigue
- abnormal dreams or nightmares
- abdominal distress
- Loss of appetite (anorexia),
- Diarrhea
- Confusion
- Dizziness
- Nightmares
- Agitation and/or depression
- Higher acute sense of sensual activities.
- Loss of appetite/ anorexia
- Nausea
- Vomiting
- Palpitations

Additional digoxin toxicity symptoms include:

- Decreased consciousness
- Decreased urine output
- Difficulty breathing when lying down
- Excessive night time urination
- Generalized body swelling,

Examinations and tests:

The heart rate may be rapid or slow and may be irregular.

An ECG is done to check for irregular heart beats.

Blood tests will be done to check:

- BUN and creatinine (which help reveal kidney function)
- Digoxin and digitoxin levels
- Potassium level

- Magnesium level
- Blood chemistry
- Digoxin - test
- Digitoxin - test

Treatment:

In an emergency, assist breathing as needed and get professional medical help.

Arrhythmias are treated according to which arrhythmia develops.

If toxicity is due to a recent, acute single exposure, treatment may involve:

- Activated charcoal
- Tube through the mouth into the stomach to wash out the stomach (gastric lavage)

Digitoxin blood levels may be lowered with repeated doses of charcoal, given after gastric lavage.

Methods to cause vomiting are usually not performed because vomiting can worsen slow heart rhythms.

In severe cases, medications called digoxin-specific antibodies may be prescribed. Hemodialysis may be required to reduce the levels of digitalis in the body.

Prevention:

Digitalis blood levels should be monitored regularly if you are taking digitalis medications. Blood chemistries should also be monitored to detect conditions that make digitalis toxicity more common.

Potassium supplements may be prescribed if you take diuretics and digitalis together, or a potassium-sparing diuretic may be prescribed.

Precipitating or risk factors to digoxin toxicity:

The most common precipitating cause of digitalis intoxication is depletion of potassium stores, which occurs often in patients with heart failure as a result of diuretic therapy and secondary hyperaldosteronism. Also reduced kidney function will cause digitalis to build up in the body rather than be removed normally through urine. Therefore, any disorders that disrupt kidney functioning (including dehydration) make digitalis toxicity more likely.

Other factors that would increase digoxin toxicity include:

- Advanced age
- Myocardial infarction or ischemia
- Hypothyroidism
- Hypercalcemia
- Renal insufficiency

Case study:

A 4-year child brought to the hospital by his mother who found him playing with an open bottle of her heart medicine. He complained of nausea, vomiting, diarrhea and blurred vision. The heart pill was identified as digoxin 0.25 mg.

1- ***What is the mechanism of digoxin toxicity?***
2- ***Can hemodialysis facilitate drug elimination? Why?***
3- ***How does chronic toxicity occur?***
4- ***What is the Fab antibody?***

Heavy Metal Poisoning

- Arsenic Poisoning
- Cadmium Poisoning
- Lead Poisoning
- Mercury Poisoning

Heavy metal poisoning is the accumulation of heavy metals, in toxic amounts, in the soft tissues of the body. Symptoms and physical findings associated with heavy metal poisoning vary according to the metal accumulated. Many of the heavy metals, such as zinc, copper, chromium, iron and manganese, are essential to body function in very small amounts. But, if these metals accumulate in the body in concentrations sufficient to cause poisoning, then serious damage may occur.

The heavy metals most commonly associated with poisoning of humans are *lead, mercury, arsenic and cadmium.* Heavy metal poisoning may occur as a result of industrial exposure, air or water pollution, foods, medicines, improperly coated food containers, or the ingestion of lead-based paints.

Signs & Symptoms

The symptoms of heavy metal poisoning vary according to which type of metal overexposure is involved. Some specific examples are:

I- **ARSENIC POISONING**

Source of exposure: A well-known poison used throughout history. It is used in the manufacture of pesticides. Naturally occurring arsenic contamination of drinking water is a worldwide problem, food fish, shellfish, meat, poultry, dairy products and cereals can also be dietary sources of arsenic, although exposure from these foods is generally much lower compared to exposure through contaminated groundwater. In seafood, arsenic is mainly found its less toxic organic form.

Forms:

The gas from arsenic also has some industrial uses. It is the most toxic form of arsenic. Inhalation of over 10 ppm is lethal and at concentrations higher than 25 ppm is reported to be lethal in less than an hour after exposure, while over 250 ppm is reported to be instantaneously lethal.

Inorganic arsenic absorbed orally, of the inorganic arsenic compounds, arsenic trioxide, sodium arsenite and arsenic trichloride are the most common trivalent compounds, and arsenic pentoxide, arsenic acid and arsenates (e.g. lead arsenate and calcium arsenate) are the most common pentavalent compounds. Inorganic arsenic and arsenic compounds are considered to be cancer-causing chemicals. Arsenite, is more toxic than arsenate, or As^{+5}.

Characters: Arsenic is tasteless, odorless and is well absorbed by the respiratory & GI tracts and distributed to all body tissues.

Mechanism of toxicity

Arsenic (all forms):

• Inhibit –SH enzymes (pyruvate dehydrogenase (glycolysis) is exquisitely sensitive. This enzyme system is necessary for mitochondrial oxidative phosphorylation. Uncouple mitochondrial oxidative phosphorylation take places.

• Damages epithelial linings of respiratory & GI, CNS, liver, bone marrow & skin

• Arsenic may substitute phosphates in high energy compounds.

• Arsine gas (AsH3) causes severe hemolysis and hemoglobinuria.

• Certain cancers have been linked to Arsenic such as lung, bladder, skin, leukemia, and lymphoma.

Arsenic Overexposure may cause:

Headaches, drowsiness, confusion, seizures, and life-threatening complications.

Neurological symptoms include brain damage (encephalopathy), nerve disease of the extremities (peripheral neuropathy), pericapillary hemorrhages within the white matter, and loss or deficiency of the fatty coverings (myelin) around these nerve fibers (demyelination).

Skin problems include transverse white bands on the fingernails (mees' lines) and excessive accumulation of fluid in the soft layers of tissue below the skin (edema).

Gastrointestinal symptoms include (gastroenteritis) that is characterized by vomiting; abdominal pain; fever; and diarrhea, which, in some cases, may be bloody. Other symptoms include breakdown of the hemoglobin of red blood

cells (hemolysis), a low level of iron in the red blood cells (anemia), and low blood pressure (hypotension).

Some individuals may experience a garlic-like odor that may be detectable on the breath.

In cases of chronic poisoning, weakness, muscle aches, chills, and fever may develop. The onset of symptoms in chronic arsenic poisoning is about two to eight weeks after exposure. Skin and nail symptoms include hardened patches of skin (hyperkeratosis) with unusually deep creases on the palms of the hands and the soles of the feet, unusual darkening of certain areas of the skin (hyperpigmentation), transverse white bands on the fingernails (mees' lines), and a scale like inflammation of the skin (exfoliative dermatitis).

Other symptoms include inflammation of sensory and motor nerves (polyneuritis) and the mucose membrane lining the throat.

Inorganic arsenic accumulates in the liver, spleen, kidneys, lungs, and gastrointestinal tract. It then passes through these sites but leaves a residue in tissues such as skin, hair, and nails. Symptoms of acute inorganic arsenic poisoning include severe burning of the mouth and throat, abdominal pain, nausea, vomiting, diarrhea, low blood pressure (hypotension), and muscle spasms. Individuals with severe inorganic arsenic poisoning may experience heart problems (cardiomyopathy); accumulation of acid in the tubes of the kidneys (renal tubular acidosis); breakdown of the hemoglobin of red blood cells (hemolysis); irregular heart rhythms (ventricular arrhythmias); coma; seizures; bleeding within the intestines (intestinal hemorrhage); and

yellowing of the skin, mucous membranes, and whites of the eyes (jaundice).

Treatment –Acute poisoning: Induce emesis, and gastric lavage -Arsenic toxicity with significant GI and CNS symptoms is treated with chelating agents: BAL, and DMSA (Succimer) -Arsine gas: Chelation is ineffective, blood transfusion for anemia and dialysis if renal dysfunction develops.

II- Lead

Source of exposure:

Major routes of exposure are ingestion or inhalation

Lead production workers, battery plant workers, welders and solders may be overexposed to lead if proper precautions are not taken.

Lead is stored in the bone but may affect any organ system.

• Lead based paints in old homes or commercial sites (only paints used in household applications are lead free)

• Industrial wastes

Occupational exposure to lead in painting, smelting, firearms instruction, automotive repair, brass or cooper foundries, printing, battery manufacturing, mining, gasoline, glass, and bridge, tunnel and elevated highway construction may also occur.

Another cause of lead poisoning is through the contamination of water from lead pipes.

Additional causes of lead poisoning include calcium products, progressive hair dyes, kajal, surma, kohl, and foreign digestive remedies.

• Lead-glazed ceramics

Lead pharmacokinetics

Metallic lead is slowly but consistently absorbed by all routes except through the skin. Absorption of lead dust via the respiratory tract is the most common cause of industrial poisoning. The intestinal tract is the primary route of entry in non-industrial exposure. Absorption via the gastrointestinal tract varies with the nature of the lead compound, but in general, about 10% of ingested inorganic lead is absorbed. Ingested lead is excreted in stool (90%) and urine. Lead also eliminated through sweat and mother's milk. It may also appear in hair, nails and saliva.

Mechanism of toxicity

• Most lead in the blood is bound to RBCs but is also stored in soft tissue (brain & kidney) and bone. Tissue t1/2 = 20-30 years.

• Binds to sulfhydryl groups, impairs a number of metabolic processes particularly hemoglobin synthesis also contributes to RBCs fragility.

• Lead is structurally similar to Calcium and interferes with Ca^{+2} mediated processes.

• Children absorb 40-50% of ingested lead and are symptomatic at lower levels than adults; adults absorb 10-15%.

Clinical Presentation

The effects of lead poisoning varies depending on the age of the individual and the amount of exposure.

In children, symptoms vary depending upon the degree of exposure to lead. Symptoms usually develop over a three to six week time period. Children to

be less playful, clumsier, irritable, and sluggish (lethargic). Headaches, vomiting, abdominal pain, lack of appetite (anorexia), constipation, slurred speech (dysarthria), changes in kidney function, unusually high amounts of protein in the blood (hyperproteinemia), and unusually pale skin (pallor) resulting from a low level of iron in the red blood cells (anemia). Neurological symptoms associated with lead overexposure include an impaired ability to coordinate voluntary movements (ataxia), brain damage (encephalopathy), seizures, convulsions, swelling of the optic nerve (papilledema), and/or impaired consciousness. Some affected children experience learning or behavioral problems such as mental retardation and selective deficits in language, cognitive function, balance, behavior, and school performance. In some cases, symptoms may be life-threatening.

In adults, overexposure to lead may cause high blood pressure and damage to the reproductive organs. Additional symptoms may include fever, headaches, fatigue, sluggishness (letheragy), vomiting, loss of appetite (anorexia), abdominal pain, constipation, joint pain, loss of recently acquired skills, incoordination, listlessness, difficulty sleeping (insomnia), irritability, altered consciousness, hallucinations, and/or seizures. In addition, affected individuals may experience low levels of iron in the red blood cells (anemia), peripheral neuropathy, and, in some cases, brain damage (encephalopathy). Some affected individuals experience decreased muscle strength and endurance; kidney disease; wrist drop; and behavioral changes such as hostility, depression, and/or anxiety. In some cases, symptoms may be life-threatening.

General symptoms:

• Multi-systems involvement:

• GI symptoms: anorexia, pain, vomiting, constipation, GI muscle spasm (lead colic).

• Anaemia

• Neurologic symptoms: headache, fatigue, irritability, tremor, ataxia, encephalopathy, coma

• Peripheral neuropathy (more motor than sensory) (vs. arsenic), Presents classically as wrist-drop which is painless weariness of the extensor muscle of the hand.

• Renal dysfunction

• Reproductive effects include stillbirth, cognitive dysfunction in children, spontaneous abortion, and infertility (both male & female).

Treatment

-Treatment is based on BLL, age, severity of symptoms.

-Asymptomatic adults (usually the parents of symptomatic children) may not require treatment if source is removed, follow BLL over time.

-Low BLL (<45µg/dl): Oral DMSA (the agent of choice unless nausea/vomiting, severe toxicity or encephalopathy)

-Encephalopathy regardless of BLL: BAL (IM) + EDTA (IV)

-Symptomatic adults, BLL >100 μg/dl, symptomatic children, BLL>70 μg/dl: BAL (IM)+EDTA (IV)

-All with elevated BLL must have frequent follow up BLLs to prove therapeutic effect and/or elimination of exposure. Continue treatment until BLL reach “normal” levels

III. Cadmium

• Cadmium is a chemical element that found in the nature in close association with zinc.

Cadmium is used for many items, including electroplating, storage batteries, vapor lamps and in some solders. The onset of symptoms may be delayed for two to four hours after exposure.

• Cadmium and zinc are similar in structure and cadmium tends to displace zinc in enzymatic and organ functions.

• The cadmium/zinc ratio is important in the development of cadmium toxicity; the storage of cadmium is much greater in the face of zinc deficiency while adequate zinc levels can mitigate cadmiums effects.

• Cadmium is absent from neonates and peaks in concentration at 50 years of age due to accumulation from the environment.

• Cadmium does not cross the placenta, nor secreted in breast milk.

• Cd is not well absorbed from the GI tract (~20%), it is stored primarily in the kidney, liver and testis.

Sources

• Cigarette smoke (the common source for most individuals)

• Batteries

• Refined foods (During growth cereal grains concentrate Cd from the soil along with Zn; refinement of these grains removes the Zn but leaves the Cd)

• Water pipes, and galvanized metals

• Coal

• Shell fish

• Ceramics (glaze)

• Dental materials

• Cereal grains & root vegetables

• Industrial workers, metal workers, zinc & lead miners and those working with galvanized metal products are at risk for Cd accumulation to toxic levels. The risk increases when combined with smoking or exposure to 2nd hand smoke.

Symptoms:

Overexposure may cause fatigue, headaches, nausea, vomiting, abdominal cramps, diarrhea, and fever. In addition, progressive loss of lung function (emphysema), abnormal buildup of fluid within the lungs (pulmonary edema), and breathlessness (dyspnea) may also be present. In some cases, affected individuals may exhibit increased salivation; yellowing of the teeth; an unusually rapid heart beat (tachycardia); low levels of iron within the red blood cells (anemia); bluish discoloration (cyanosis) of the skin and mucous membranes due to insufficient oxygen supply to these tissues; and/or an

impaired sense of smell (anosmia). Individuals with cadmium poisoning may also experience improper functioning of the canals with the kidney (renal tubular dysfunction) characterized by excretion of abnormally high levels of protein in the urine (proteinuria), minor changes in liver function, and/or softening of certain bones (osteomalacia).

Mechanism of toxicity

• Cd competes with zinc for binding sites and interferes with zinc's essential functions (enzyme co-factor), it also can acts as a catalyst in oxidation reactions producing free radicals. Cd toxicity is exacerbated when concomitant Zn deficiency occurs.

• Acute exposure to Cd may cause flu like syndrome with fever, chills and myalgias (The Cadmium Blues). More severe exposures can cause upper airway inflammation, pneumonitis and pulmonary edema.

• Concentration in the kidneys can result in renal hypertension, calcium renal-lithiasis (renal stone) and proteinuria and eventually renal failure (often the cause of death from Cd poisoning).

• Cd appears to depress immune function particularly in response to viral and bacterial infections.

• Cd affects bones resulting in a painful osteomalacia progressing to osteoporosis, it can also cause gout. Itai-itai disease (literally: "ouch-ouch" disease) was caused by the documented cases of mass cadmium poisoning in Toyama after 2nd war. The disease is named for the severe pains (Japanese:

itai) caused in the joints and spine. The term itai-itai disease was coined by locals.

• Cd exposure is directly implicated in some cancers; lung cancer with inhaled Cd.

Treatment

• Isolate form the source.

• Zinc supplementation may promote Cd excretion.

• Intravenous EDTA a chelating agent is indicated when toxic levels are attained.

• Iron, copper, selenium and vitamin C supplementation may promote Cd excretion.

• BAL is avoided as it forms a complex with Cd that may lead to renal toxicity.

MERCURY POISONING

Mercury is used by dental assistants and hygienists, and chemical workers. Mercury contaminated fish are a major concern throughout the world.

Forms of Mercury

Mercury exists in three forms: elemental, inorganic and organic

– Elemental mercury, “quicksilver” is poorly absorbed across the GI tract but results in a significant inhalation exposure.

– Inorganic mercury is corrosive and primarily absorbed across the GI tract. Batteries (HgCl2 more toxic than HgCl) Pesticides, Amalgams

– Organic mercury (mostly methyl mercury) is found in seafood & shellfish. Rapidly absorbed across the GI tract and distributed to the CNS.

Sources of Exposure

• Food treated with mercurial fungicides

• Dental amalgams

• Amalgam manufacturers

• Thimerosal (vaccine preservative)

• Batteries

• Fish from contaminated waters

• In the manufacturing of thermometers, mirrors, incandescent lights, x-ray machines, and vacuum pumps.

• Dyes

Another cause of mercury poisoning is contaminated water and fish. Children often are exposed to mercury through paint, calomel, teething powder, and mercuric fungicide used in washing diapers.

Mechanism of mercury toxicity

Mercury ions produce toxic effect by protein precipitation, enzyme inhibition and generalized corrosive effects. Mercury binds to sulfhydryl groups and rendering numerous proteins inactive.

Clinical Presentation

Mercury can affect the lungs, kidneys, brain, and/or skin. Symptoms of mercury poisoning include fatigue, depression, sluggishness (letheragy), irritability, and headaches.

Respiratory symptoms associated with inhalation to mercury vapors include coughing, breathlessness (dyspnea), tightness or burning pain in the chest, and/or respiratory distress. Some affected individuals may experience abnormal buildup of fluid in the lungs (pulmonary edema); pneumonia; and/or abnormal formation of fibrous tissue (fibrosis).

There may be behavioral and neurological changes associated with overexposure to mercury poisoning, such as excitability and quick-tempered behavior, lack of concentration, and loss of memory. Shock and permanent

brain damage may also be result from mercury poisoning. Some affected individuals experience mental confusion. A progressive cerebellar syndrome with impaired ability to coordinate voluntary movements (ataxia) of the arms may also be present. Abnormal involuntary movements of the body such as uncontrolled jerky movements combined with slow, writhing movements (choreoathetosis) are common. Additional symptoms include non-inflammatory degenerative disease of the nerves (polyneuropathy); impaired ability to coordinate voluntary movements (cerebellar ataxia); tremors of the legs and arms and, in some cases, of the tongue and lips; seizures; and/or slurred speech (dysarthria). Changes in mood, behavior, and consciousness may also occur.

In some cases of chronic exposure to inorganic mercury a personality disorder known as erethism or mad hatter syndrome may occur. Symptoms associated with mad hatter syndrome include memory loss, excessive shyness, abnormal excitability, and/or insomnia. This syndrome was described in workers with occupational exposure to mercury in the felt-hat industry.

Many affected individual experience sensory impairments such as visual problems (e.g. constriction of visual fields, tunnel vision, and blindness) as well as hearing loss.

Some individuals may experience skin changes such as painful swelling and pink coloration of the fingers and toes (acrodynia); persistent redness or inflammation of the skin (erythema); extreme sensitivity (hyperesthesia) of the affected areas; and tingling and sensory disturbances.

In some cases, other affected individuals may experience stomach and intestinal disturbances; kidney damage; dehydration; acute renal failure; inflammation of the gums (gingivitis); severe local irritation of the mouth and pharynx, accompanied by vomiting; and/or abdominal cramps with bloody diarrhea.

Mercury is mainly excreted through the urine and feces.

Treatment

Urine mercury levels correlate with inorganic mercury toxicity, but not organic mercury exposure (requires blood levels).

Treatment is indicated when levels reach 35µg/dl.

Elemental exposure requires monitoring of respiratory function.

Inorganic mercurial salts are corrosive; evaluation of the complete GI tract is indicated.

Chelating Agents

• Chelating Agents: drugs used to prevent or reverse the toxic effects of heavy metals on enzymes or other cellular targets through competitive binding of metals.

• Chelators contain 2 or more electronegative groups (-OH, -SH, -NH) that form stable coordinate covalent bonds with cationic metal ions.

• The efficiency of the chelator is partly determined by the number of ligands available for metal binding. The greater the number of metal-ligand bonds. The more stable the metal-chelator complex the more efficient the removal.

• Depending on the number of metal-ligands bonds, the complex may be referred to a: mono -, bi-, or polydentate.

An ideal chelating agent should have the following properties:

1. High water solubility

2. Resistance to metabolic degradation

3. Ability to reach metal storage sites in the body

4. Capacity to form stable, nontoxic complexes with toxic metal at pH of body fluids. These complexes should be excreted easily through urine or feces

5. A low affinity for Ca2+ and other endogenous ligand to avoid adverse effects like hypocalcaemia, zinc and magnesium depletion.

Commonly Used Chelating Agents

Chelating Agent	*Metal*	*Notes*
BAL (British Anti-Lewisite) Dimercaprol	As, Pb, Hg	Promotes redistribution of As & Hg to CNS in chronic exposure
Succimer (Dimercaptosuccinic acid, DMSA)	As, Pb, Hg	Oral form of BAL, agent of choice in pediatric Pb.
Unithol	Hg, As, Pb	Fewer side effects than Succimer
Ethylenediaminetetraacetic acid (EDTA)	All +2 & +3 cations (transition metals) Mainly used for Pb.	Given IV, nephrotoxic so increase fluid intake during treatment.
Penicillamine	Cu++ in Wilson's disease, Hg, adjunct in Pb & As	Oral agent
Desferoxamine	Fe only	

1. Dimercaprol (BAL)

Dimercaprol (2,3-dimercapto-1-propanol) was discovered during World War II, originally as an antidote for poisonous arsenical gas "Lewisite". Hence it is also known as British Anti-Lewisite (BAL).

Dimercaprol (BAL) is colorless and only liquid with an offensive odor of rotten eggs. It is soluble in water, but aqueous solutions are unstable and oxidize readily. Dimercaprol is therefore dispensed in 10% solution in peanut oil and must be administrated intramuscularly. It interacts directly with metals in blood and tissue fluids and reactivates, sulfhydryl containing enzymes.

Dimercaprol is used mainly for the treatment of mercury, lead and arsenic poisoning. It is contraindicated in iron poisoning as BAL-Fe complex that is formed is itself toxic.

Two dimercaprol molecules make a complex with single mercury atom and this complex is then excreted in urine. However, the urine must be kept alkaline to avoid dissociation of the complex and subsequent reabsorption of metal. The local release of metal ions can also cause renal toxicity.

The recommended dose schedule is 5 mg/kg I.M. followed by 2-3 mg/ kg /8 h for 2 days and then once a day for 10 days.

Adverse effects include pain at the site of injection, tachycardia, mild increase in BP, vomiting, tingling and burning sensation in extremities, sweating, cramps and headache.

2. Succimer

It is (2,3- dimercapto succinic acid), a structural analogue of dimercaprol. Unlike dimercaprol it is orally effective, less toxic and more water soluble.

It is more specific for lead chelation than dimercaprol. It also reduces mercury contents of kidney, a key target organ for accumulation of mercury salts.

Adverse effects include anorexia, vomiting and diarrhea. It has negligible impact on the body stores of calcium, iron and magnesium.

3. Edetate Calcium Disodium (Ethylene Diamine Tetra-acetic Acid, EDTA Disodium Salt)

Edetate calcium disodium complex is a chelator for many divalent (Pb, Zn, Cd, Mn and Hg) as well as trivalent (Fe) metals. In this exchange process, its own calcium is displaced from the molecule.

The parent compound ethylene diamine tetra acetic-acid is a stronger chelator for Ca^{2+}, which may produce life-threatening hypocalcaemia as a side effect. This limitation has been circumvented by using disodium calcium salt of EDTA

Edetate Calcium Disodium is a highly polar compound, does not cross BBB and poorly crosses cell membranes thus serving primarily as an extracellular rather than an intracellular chelator.

It is not absorbed from GIT thus given parentally. I.M. injection is very painful; hence, usually given by slow I.V. injection.

Edetate Calcium Disodium is mainly indicated for lead poisoning as well as other heavy metals also could be used for poisoning with zinc, magnesium.

It is not effective in treatment of mercury poisoning, as mercury is too tightly bound by SH group and sequestrated in the body tissue that is not penetrated by **EDTA.**

EDTA toxicity

EDTA is toxic to the kidney, and the renal tubules appear relatively sensitive to its toxic effects, which include degeneration of the proximal tubules, progressing into total destruction (Can be prevented by maintaining adequate urine flow, limitation of doses and treatment period). The effects on kidney disappear with cessation of therapy.

Other toxic effects have been observed also, including chills, fever, nausea, vomiting, myalgia, allergic reactions, and glucosuria.

4. D-Penicillamine

D-Penicillamine (dimethylcystein or 3-mercapto-D-valine) is a water soluble degradation product. Its D-isomer (instead of L-isomer) is less toxic and highly effective chelator of copper.

It is a drug of choice in the management of Wilson's disease.

It can be used to treat lead or mercury poisoning but succimer is more preferred.

It is also used to treat cystinuria (cystine stone) as it complexes with cystine and prevents its precipitation in urinary tract.

It is also occasionally used for the treatment of rheumatoid arthritis.

Its recommended dose schedule in the treatment of Cu poisoning is 500 mg twice a day, 2 hrs after meal (to avoid chelation of other dietary metals).

Adverse effects include hypersensitivity, proteinuria (rare), leucopenia and aplastic anemia (careful monitoring is beneficial).

V. IRON

Sources of poisoning:

Many different iron preparations are commercially available, with variable amounts of elemental iron. The three most common preparations are ferrous gluconate, sulfate and fumarate with 12%, 20% and 33% elemental iron by weight, respectively. Chewable pediatric multivitamins with iron contain up to 15 mg of elemental iron per tablet but toxicity may occur when large quantities are ingested. Ferrous sulfate is the most commonly used iron preparations and the iron salt most frequently involved in poisonings. Ingestions of less than 20 mg/kg of elemental iron usually produce insignificant intoxication. Ingestions of 20-60 mg/kg are potentially toxic, and ingestion of 60 mg or more are generally toxic. The estimated lethal dose of elemental iron required for acute iron poisoning is between 200-250 mg/kg.

Pathophysiology:

Iron Homeostasis is complex, mainly involving intake, stores and loss. Generally, about 2 to 15 percent is absorbed from the gastrointestinal tract, whereas iron elimination accounts for only 0.01 percent per day. During periods of increased iron need (childhood, pregnancy and blood loss) absorption of iron is increased greatly. Absorbed iron is bound to the plasma protein transferring for transfer to storage sites in hemoglobin, myoglobin and iron-containing enzymes and the iron storage proteins ferritin and hemosiderin. Normally excess ingested iron is excreted and some is contained within shed intestinal cells, in bile and urine, and even smaller amounts in sweat, nails and hair.

Clinical manifestations:

The clinical effects of serious iron poisoning can be divided into five stages.

Stage I (0.5-6 hours):

Symptoms usually occur within 6 hours of ingestion and are characterized by nausea, vomiting, diarrhea and abdominal pain. Direct corrosive effects of iron result in gastrointestinal mucosal injury. Shock due to blood or fluid loss leads to hypoperfusion which may contribute to the development of metabolic acidosis. Release of hydrogen ions when iron is oxidized from the ferrous to the ferric form may also contribute to acidosis. CNS symptoms may include lethargy, coma or convulsions.

Stage II (6-24 hours):

Some patients may enter a transient phase of improvement, which usually lasts less than 24 hours (latent stage) and the toxicity may end with this stage for those who have ingested small amounts of iron. During this stage the serum iron is unloaded to intracellular sites, where toxicity may manifest in the third stage.

Stage III (4-40 hours):

If a large amount of iron was ingested, the latent stage will progress to a third stage of metabolic dysfunction, cardiovascular collapse and hepatic, renal and neurologic failure. Acute bowel perforation and infarction may occur anywhere from the stomach to the jejunum. Aggressive intervention, with antidotal therapy and hemodynamic support, is essential during this stage of toxicity.

Stage IV (2-4 days):

This stage consists of hepatic failure, which may occur 2-3 days following severe iron poisoning. It is thought to result from direct uptake of iron by the reticuloendothelial system in the liver.

Stage V (several weeks):

This stage of iron toxicity only rarely occurs. Gastric outlet obstruction secondary to strictures and scarring from the initial corrosive injury can develop 2-8 weeks following ingestion.

Laboratory Diagnosis:

1- Deferoxamine test: It is performed by mixing 2 mL of gastric fluid with two drops of 30% hydrogen peroxide. Then deferoxamine is added. If iron is present, a deferoxamine-iron complex (ferrioxamine) is formed and turns the solution orange-red.

2- Serum iron determination: Normal serum iron concentrations range 50 to 150 μg/dl. Levels over 350 μg/dl are usually associated with signs of toxicity. Significant toxicity frequently accompanies iron concentration between 500 and 1000 μg/dl. Levels over 1000 μg/dl are associated with considerable morbidity.

3- Other laboratory tests: Serum electrolytes, complete blood count, blood sugar, blood urea nitrogen, creatinine, arterial blood gases, and liver and kidney function tests.

Treatment:

1- Decontamination: Undissolved tablets should be removed from the stomach by ipecac-induced emesis. Gastric lavage with sodium bicarbonate solution forms insoluble ferrous carbonates and decreases additional iron absorption. Gastric lavage with sodium dihydrogen phosphate is no longer recommended because of the high frequency

of side effects (hypocalcemia, hyperphosphatemia and acidosis) associated with its use. Gastric lavage with deferoxamine is not recommended as it has not been proven effective and may enhance iron absorption. Usually, deferoxamine solution for lavage is reserved only for patients demonstrating sever toxicity or in those with serum iron exceeding 500 μg/dl. Activated charcoal is of no benefit and should only be administered if a mixed ingestion is suspected. The use of whole bowel irrigation has been reported with successful decontamination in a number of cases.

2- Antidote: A serum iron concentrations that is greater than 500 μg/L or the development of seizures, shock or coma are indications for chelation therapy with deferoxamine (desferal). Deferoxamine is usually given by intravenous and intramuscular routes. The recommended dose is 36 mg/kg/h and daily dose should not exceed 6 g. Rusty-red colored urine following treatment with deferoxamine is classically referred to as the vin rose urine change. This color change is due to the presence of ferrioxamine, the product of iron chelation with deferoxamine. Deferoxamine, a byproduct produced by *Streptomyces pilosus*, is a highly specific chelator of free iron in the ferric form. A dose of 100 mg will chelate approximately 9 μg of elemental iron. Deferoxamine may also bind ferritin, hemosiderin and iron within the reticulo-endothelial system; it will not bind iron in hemoglobin or in cytochrome P450 mixed-function oxidase system.

3- Supportive measures: Hypotension should be treated with norepinephrine or dopamine. Hemodialysis or peritoneal dialysis do not effectively remove elemental iron.

Case study:

A 17-year old female presents to the emergency department 6 h after she had ingested a large number of ferrous sulphate tablets. On admission, she was diaphoretic, lethargic and complained of abdominal pain, nausea and vomiting.

1- ***In which stage of iron intoxication the patient might be?***
2- ***Discuss the mechanism by which iron poisoning causes an elevated anion gap metabolic acidosis.***
3- ***How can you manage such toxicity case?***

ORGANOPHOSPHATE INSECTICIDES

Poisoning from exposure to organophosphates is common in rural areas and in developing countries. They are efficiently absorbed by inhalation, ingestion, and skin penetration. Examples of these groups are parathion, methyl parathion, malathion and diazinon.

Mechanism of toxicity:

Organophosphates insecticides produce their toxic effects via inhibition of nervous tissue acetylcholinesterase (AChE) enzyme. This enzyme is responsible for the destruction and termination of the biological activity of the neurotransmitter acetylcholine (Ach). Loss of enzyme function leads to accumulation of Ach peripherally at the nerve ending cholinergic neuroeffector junctions (muscarinic effects), skeletal nerve-muscle junctions, and autonomic ganglia (nicotinic effects), as well as centrally. The inactivation of AChE occurs in several stages and becomes irreversible after 24-36 hours.

Clinical manifestation:

1- Stimulation of muscarinic receptors produce a clinical picture best remembered by the menemonic **DUMBBELS:** *Diarrhea, Urinary incontinence, Miosis, Bradycardia, Bronchospasm and bronchorrhea, Emesis, Lacrimation, Salivation*. In addition to bradycardia, cardiac conduction disturbances can result from augmental vagal tone.

2- Stimulation of nicotinic receptors at the neuromuscular junction causes muscle weakness, fasciculation and paralysis. Effects at ganglionic nicotinic receptors result in diaphoresis, mydriasis,

tachycardia and hypertension, which most often appear early in the course of poisoning.

3- CNS effects include anxiety, restlessness, lethargy, confusion, psychosis, coma and seizures. Death from organiophophate poisoning occurs secondary to respiratory failure and cardiovascular collapse.

Laboratory diagnosis:

1- Gas chromatographic techniques can detect organophosphate metabolities of malathion, parathion and diazinon in both blood and urine.

2- Blood samples should be drawn to measure plasms pseudocholinesterase and red blood cell AChE levels. Both types are inhibited by organophosphates but inhibition of erythrocyte AChE is more reliable index of organophosphate poisoning.

3- Depressions of plasma pseudocholinesterase and/or RBC acetylcholinersterase enzyme activities are generally available biochemical indicators of excessive organophosphate absorption.

Management of toxicity:

1- General measures:

a- Airway protection: Intubate the patient and aspirate the pulmonary secretions with a large-bore suction device. It may be necessary to support pulmonary ventilation with artificial respiration for several days. Tissue oxygenation is essential prior to atropine administration, so as to minimize the risk of ventricular fibrillation associated with hypoxia.

b- Skin decontamination: Because organophosphate may be absorbed through intact skin, contaminated clothing, including shoes, should be

removed and treated as toxic waste. Skin should be cleaned with large amounts of water and mild soap.

c- Gastrointestinal decontamination: Gastric lavage with a large-bore orogastric tube may be performed with care taken to prevent aspiration. Ipecac-induced emesis should be considered if spontaneous vomiting has not already occurred. A cathartic (e.g sorbitol or magnesium citrate) can be administered once unless diarrhea has occurred. Activated charcoal can also be given for GIT decontamination.

d- Convulsions can be controlled with intravenous diazepam, Phenobarbital or phenytoin.

2- Antidotes

a- Atropine: It is a competitive antagonist of Ach at muscarinic receptors, both in the peripheral nervous system and CNS. Atropine has no effect on nicotinic receptors. It is effective against muscarinic manifestations, but it is ineffective against nicotinic actions, specifically muscle weakness and twitching, and respiratory depression. Administer atropine sulfate (2 mg intravenously or intramuscularly) and repeat every 3-8 minutes until signs of atropinization appear (flushed face, dry mouth, dilated pupils and fast pulse).

b- Glycopyrolate: It can be used as an alternative to atropine (minimal CNS effects). Ampules of 7.5 mg of glycopyrolate were added to 200 mL of saline and given by intravenous infusion.

c- Pralidoxime (2-hydroxyiminomethyl 1-methyl pyridinum chloride, 2-PAM): Pralidoxime is a specific antidote that effectively reverses phosphorylation of the cholinesterase when given within 48 hours post-exposure. It works by attaching onto the phosphorylated enzyme and removing the phosphate moiety of the organophosphate-enzyme complex to regenerate AChE. It reverses both nicotinic and muscarinic effects of

organophosphate toxicity. In adults, the initial dose is 1-2 gm, given intravenously over 30 minutes. After the initial dose, a continuous of 500 mg/hours is sufficient to serum levels in most cases. Side effects of PAM are minimal with recommended doses. At higher doses or rapid administration, respiratory and cardiac arrest, diastolic hypertension, dizziness and blurred vision have been reported.

Case study:

A 37-year-old man was brought to the hospital after ingestion of 120 ml of the insecticide parathion in a suicide attempt. On admission the patient was unresponsive with grand mal seizures and had respiratory compromise from excessive pulmonary secretions.

1- ***What is the mechanism underlying such intoxication?***
2- ***What are the clinical manifestations that most likely occur?***
3- ***How can you manage such toxicity case?***

ANIMAL POISONS

Animal toxins are a complex mixture of *polypeptides*, *enzymes* and *chemicals* which can cause cellular injury. Several mechanisms are involved in pathophysiology of venom poisoning. Direct injury can be induced by chemicals, enzymes and polypeptides. *Polypeptides* exert their effect through action on ion channels and receptors on the cell membrane. The action of *polypeptides* upon ion channels and receptor sites of excitable membranes through signal transduction causes the release of neurotransmitters which results in neuromuscular effects. *Enzymes* can cause membrane lysis, pore formation, cytoskeletal destruction, and release inflammatory and vasoactive mediators with action on the coagulation pathway at various levels. *Proteolytic enzymes* and phospholipase A2 are important causes of cellular injury and coagulopathy. Indirectly, animal enzymes, especially phospholipase A2 and metalloproteases, can induce the release of vasoactive mediators and proinflammatory cytokines which can lead to hemodynamic alterations and cause organ injury. Cardiovascular symptoms are therefore common. They can also trigger the inflammatory process with generation of adhesion molecules, complement activation, acute phase proteins, free radicals, increased vascular permeability and increased blood viscosity. Local reactions include pain, swelling and redness. Hemodynamic changes may result if the process is severe. Immunologic reaction usually manifests in the form of allergic response such as skin rashes and edema. In the severe form, anaphylaxis with respiratory and cardiovascular symptoms may occur.

Ion transport and neurotransmitters

Several animal toxins act on ion channels causing either polarization or depolarization of excitable membranes which affects the action potential and neuromuscular function. Intracellular calcium regulated by Ca channels controls neurotransmitter secretion and release. Opening of Ca channels by depolarization or ligand stimulation increases intracellular Ca and releases neurotransmitters. On the contrary, closing of Ca channels by toxins or hyperpolarization decreases neurotransmitter secretion. Activation of Na channels and closing of K and chloride channels cause depolarization. Opening of K and chloride channels and closing of Na channels result in hyperpolarization. Snake venoms cause neuromuscular symptoms through effects on ion channels.

Enzymes and inflammatory mediators

Cellular injury can be induced by enzymes especially phospholipase A2 (PLA2) and proteases on the cell membrane. Phospholipases A2 are enzymes that catalyze the hydrolysis of the 2-acylester bond of phosphoglycerides. Phospholipases A2 are categorized into three classes. Cellular injury caused by PLA2 results in hemolysis, rhabdomyolysis, endothelial necrosis, renal tubular, and neuronal damage. PLA2 and proteases can cause a cascade effect at various levels of blood coagulation causing bleeding diathesis. Metalloproteases can cause cytoskeleton destruction, disrupting cellular adhesion, cell damage and apoptosis. A number of proinflammatory cytokines and mediators are released in toxin poisoning by enzymes. PLA2 stimulates hypothalamus pituitary axis to increase adrenocorticotrophic hormone, corticosteroid, arginine vasopressin and acute phase response. Histamine, kinins, eicosanoids, platelet activating factor, catecholamines and endothelins are released. PLA2 is considered as a starter in the formation of prostaglandins. Zinc metalloprotease cleaves gluthathione-D-transferase, tumor necrosis factor-alpha-fusion protein (GST-TNFα) to generate biologically active TNFα. Elevations of serum TNFα, IL-1, IL-6, IL-10, IFN-γ and NO are observed in snake envenomation. Vasoactive mediators including catecholamines, dopamine, thromboxanes, angiotensin II, endothelins and prostaglandins are released. Involvement of cytokines and vasoactive mediators in snake envenoming is therefore similar to that observed in sepsis. Other inflammatory mediators include complements, free radicals and adhesion molecules. Spider and scorpion venoms also cause elevation of serum proinflammatory cytokines and mediators.

Hemodynamic alterations

Hemodynamic alterations can be induced by either toxins or endogenous vasoactive mediators from the host. Some toxins have direct vascular effects similar to endothelin. Some venom inhibits angiotensin converting enzyme and decreases blood pressure. Angiotensin II-like peptide, kinins and vasoactive intestinal peptide in amphibian skin can affect vascular resistance and blood flow. Transient changes in hemodynamics can be due to neurotransmitters such as catecholamines or acetylcholine released from the host. Catecholamine, thromboxane A2, serotonin and histamine can cause pulmonary arterial constriction and hypotension. Hypotension can be observed, and transient hypertension

can occur in jellyfish sting, spider bite, scorpion sting and snake bite. In most instances, hemodynamic changes are caused by proinflammatory cytokines and vasoactive mediators which can be severe with changes in cardiac output, systemic and renal vascular resistance. Hemodynamic changes characterized by decreased systemic vascular resistance and increased renal vascular resistance parallel those observed in sepsis involving similar proinflammatory cytokines and vasoactive mediators. The renal blood flow and glomerular filtration rate are decreased. Hypotension is common in severe poisoning. Intravascular hemolysis, hemorrhage, disseminated intravascular coagulation, myonecrosis, complement activation and free radicals further contribute to hemodynamic changes.

General clinical manifestations

Besides the local reactions which consist of pain, swelling, erythema, vesiculation and necrosis, systemic reactions induced by cytokines and vasoactive mediators can be observed. Cardiovascular symptoms are frequently seen not only from the vasoactive mediators. Venoms as enzymes, in addition to causing cellular injury, can exert effects on the coagulation cascade causing bleeding diathesis. With inflammatory reactions, specific organ injury can occur. Renal involvement is common. Immunologic reaction revealed by anaphylaxis or hypersensitivity is another clinical manifestation.

Neuromuscular involvement

Neuromuscular manifestations include dizziness, fainting, numbness, blurred vision, muscle cramps, ataxia, paralysis, muscular pain, hypersalivation, nausea, and vomiting.

Hematological involvement

Erythrocyte membrane injury induced by PLA2 can cause intravascular hemolysis. Pore information on the membrane and inhibition of Na-K ATPase can cause cell swelling further contributing to hemolysis. Intravascular hemolysis is commonly observed in snake. Snake venom enzymes, through their effects on the blood coagulation cascade, platelets and vascular endothelium, result in hemorrhagic diathesis and disseminated intravascular coagulation. Bee stings and spider bite can also cause disseminated intravascular coagulation.

Pulmonary involvement

Respiratory paralysis can occur as the result of neurotoxins acting on acetylcholine receptors or ion channels either through activation or inactivation. The effect on muscle of respiration can cause respiratory failure. The second form of pulmonary involvement is pulmonary edema secondary to hemodynamic changes and increased vascular permeability induced by cytokines and inflammatory mediators. The third form is pulmonary hemorrhage due to pulmonary capillary injury caused by metalloproteases and coagulopathy. Finally, pulmonary hypertension causing syncope can be due to catecholamine, thromboxane A2, serotonin and histamine.

Gastrointestinal involvement

Nausea, vomiting and diarrhea are common in marine toxin envenomation. Hepatitis with jaundice has been described in scorpion and spider envenomation. Multiple stings by bees, can cause severe hepatocellular injury. Pancreatitis can occur following bee stings.

Renal involvement

As a highly vascularized and excretory organ, the kidney is vulnerable to toxin poisoning. Release of proinflammatory cytokines and vasoactive mediators by toxins leading to decreased renal blood flow is fundamental in the development of nephropathy. Renal injury can also be induced by toxin enzymes especially phospholipases and metalloproteases. Other factors associated with inflammation from cellular injury including hemorrhage, hypovolemia, intravascular coagulation, intravascular hemolysis, rhabdomyolysis, complements and free radicals are additional and important insults for the kidney injury. Snake bite and multiple insect stings are therefore common causes of renal injury, and tubular necrosis is an important pathological change leading to acute renal failure. A number of toxins exert effects on ion transport in the renal tubules. Melittin from bee venom inhibits Na and phosphate reabsorption but increases Ca reabsorption in proximal tubules.

1. Snakes

Poisonous snakes are found in nearly all of the tropical and temperate areas. Snake venom is the secretion ejected from the salivary glands of different types of snakes. Bites on head and trunk are more dangerous than those on the legs. The mortality among children is twice as high as among adults. The venoms of snakes are complex mixtures of various proteins, lipids, carbohydrates and enzymes and contain

procoagulants and anticoagulants, hyaluronidase, acetylcholinesterase, cardiotoxins, haemotoxins, neurotoxins and metallic ions.

Toxicity of snake venoms:

a- Neurotoxic manifestations:

The effects of neurotoxin A and B on the central nervous system are manifested by convulsion and occasionally, psychotic behavior. The myoneural junction is also affected by neurotoxin B, which results in locomotor disturbances manifested by weakness of the muscles, fasciculations and paralysis in very extreme cases. The severity of the symptoms depends upon the potency of a particular venom and the amount of venom injected.

b- Haematological manifestations:

The bite of some snakes causes marked local swelling and pain, oedema and bleeding from the mouth, nose, eyes, lungs, gastrointestinal tract and kidneys may occur as a result of the endothelial damage of small vessels and lymphatic channels. Changes in the red blood cells and their ability to transport oxygen may result in bleeding, decrease in haemoglobin and tissue anoxia, leading to necrosis. Circulatory failure is the usual cause of death.

c- Other systemic manifestations:

These include elevation or depression of temperature, nausea, vomiting, diarrhea, pain and restlessness. Tachycardia is frequently seen and occasionally, bradycardia develops. Renal failure from acute tubular necrosis has been reported. Several snake venoms block nicotinic acetylcholine receptors at the neuromuscular junction resulting in muscular weakness and paralysis. Mamba fasciculins inhibit acetylcholinesterase, thus enhancing the action of acetylcholine.

Treatment:

- Wash the bitten area with water to remove surface venom.
- Immobilize the patients and bitten area.
- Tourniquet is applied above the bite to prevent or slow down the spread of the venom. This should not cut off the flow of blood from a vein or artery.

- Sucking out venom by mouth may harm the affected area directly. This method is not effective in removing significant amount of venom, serves to introduce the mouth flora into the wound.
- A suction device can be placed over the bite to help draw venom out of the wound without cut as it causes damage of the nerves and vessels and increases the risk of infection.
- Respiration is maintained by artificial methods and administration of oxygen if necessary.
- Blood transfusion may be useful.
- Give specific antivenom intravenously to neutralize the snake venom. Prior to administration of antivenom, sensitivity testing should be undertaken.
- Tetanus and local infection should be prevented by tetanus antitoxin and penicillin.
- Analeptics and cardiac stimulants are administrated in case of collapse.
- Transfer the victim immediately to the hospital.

2. Scorpions:

Scorpions are frequently located under rocks and buried in sand. The last segment of the tail of the scorpion is equipped with a stinger called telson. The entire tail, and particularly the terminal segment housing the stringer, is extremely mobile. The toxic effects from the sting of scorpions vary with different species, the age of the patient and to certain extent with the site of the sting. The toxicity of scorpion venom is higher than that of snakes, but the scorpion injects a much smaller amount of venom.

Toxicity of scorpion venom:

The venom causes mild tingling which spreads rapidly followed by spasm of the throat, restlessness, muscular fibrillation, abdominal cramps, convulsions and respiratory failure. The patient suffers from visual disturbances, headache and impairment of speech. The symptoms may include excessive sweating, lacrimation, polyuria with glucosuria and hyperglycaemia.

Treatment:

- Immobilize the patient and the bitten part immediately. Apply a constriction band to limit absorption of venom.
- Try to draw out the venom immediately with the extractor pump.
- Give artificial respiration with O_2 if respiration is depressed.
- Apply cold packs (10-15^{o}C) for the first few hours to help slow absorption.
- Administration of specific scorpion antivenom.
- Control convulsions by the use of diazepam.
- Inject calcium gluconate, 10 ml of 10% solution slowly intravenously, to help relieve muscular cramps.
- Narcotics are contraindicated as there is evidence that potentiate the venom.
- Atropine sulfate may be indicated to control excessive parasympathetic manifestations.
- Administer a tetanus toxoid to prevent infection.

3- Jellyfish

Jellyfish are mainly free-swimming marine animals with umbrella-shaped bells and trailing tentacles. The tentacles are armed with stinging cells and may be used to capture prey and defend against predators. Jellyfish are found all over the world, from surface waters to the deep sea. Jellyfish have been in existence for at least 500 million years, and possibly 700 million years or more, making them the oldest multi-organ animal group. Jellyfish are eaten by humans in certain cultures, being considered a delicacy in some Asian countries. Many thousands of swimmers are stung every year, with effects ranging from mild discomfort to serious injury or even death; small box jellyfish are responsible for many of these deaths. Contact with a jellyfish tentacle can trigger millions of nematocysts to pierce the skin and inject venom, but only some species' venom causes an adverse reaction in humans. The effects of stings range from mild discomfort to extreme pain and death. Most jellyfish stings are not deadly, but stings of some box jellyfish, such as the sea wasp, can be deadly. Stings may cause anaphylaxis (a form of shock), which can be fatal. Jellyfish kill 20 to 40 people a year in the Philippines alone. In 2006 the Spanish Red Cross treated 19,000 stung swimmers along the Costa Brava. Vinegar (3–

10% aqueous acetic acid) may help with box jellyfish stings, but not the stings of the Portuguese man o' war. Salt water may help if vinegar is unavailable. Rubbing wounds, or using alcohol, ammonia, fresh water, or urine is not advised as they can encourage the release of more venom. Clearing the area of jelly and tentacles reduces nematocyst firing. Scraping the affected skin, such as with the edge of a credit card, may remove remaining nematocysts. Once the skin has been cleaned of nematocysts, hydrocortisone cream applied locally reduces pain and inflammation. Antihistamines may help to control itching. Immunobased antivenins are used for serious box jellyfish stings.

4- Honey bee venom

What is honey bee venom?

Apitoxin, or honey bee venom, is a cytotoxic and hemotoxic bitter colorless liquid containing proteins, which may produce local inflammation.

What can bee venom are used for?

Uses for Bee Sting Therapy

In alternative medicine, bee sting therapy is touted for the following health problems:

- Rheumatoid arthritis
- Bursitis
- Eczema
- Headaches
- Low back pain
- Migraine
- Multiple sclerosis
- Psoriasis
- Tendonitis

Bee venom is given as a shot for rheumatoid arthritis, nerve pain (neuralgia), multiple sclerosis (MS), reducing the reaction to **bee stings** in people who are allergic (desensitization) to them (**venom** immunotherapy), swollen tendons (tendonitis), and muscle conditions such as fibromyositis and enthesitis.

How does bee venom affect the body?

Bee sting venom contains proteins that **affect** skin cells and the immune system, causing pain and swelling around the **sting** area. In people with a **bee sting** allergy, **bee venom** can trigger a more-serious immune system reaction. Sep 11, 2019

Is honey bee bite good for health?

Bee venom has powerful anti-inflammatory properties and may benefit the **health** of your skin and immune system. It may also improve certain medical conditions like rheumatoid arthritis and chronic pain. Jun 24, 2019

What kind of toxin is bee venom?

The main component of bee venom responsible for pain in vertebrates is the toxin **melittin**; histamine and other biogenic amines may also contribute to pain and itching. In one of the alternative medical uses of honey bee products, apitherapy, bee venom has been used to treat arthritis and other painful conditions.

How much bee venom is fatal?

Assuming each **bee** injects all its **venom** and no stings are quickly removed at a maximum of 0.3 mg **venom** per sting, 600 stings could well be **lethal** for such a person. For a child weighing 10 kg, as little as 90 stings could be **fatal**.

What is bee poison made of?

Bee venom is a mixture of histamine, pheromones, enzymes, peptides, amino acids and other acids, with 63 components in total. The main enzymes present are phospholipase A, hyaluronidase, and lecithinase; while the main peptides are mellitin, apamin and peptide 401.

How does bee venom help arthritis?

Scientists have found that **bee venom can** control the harmful inflammation in joints that leads to rheumatoid **arthritis**. They have shown the **venom** contains molecules that cause an increase in natural hormones in the body that regulate inflammation. Jun 27, 2010

How many people die from bee stings?

Nearly 100 American deaths are caused by **bee stings**. In fact, this number probably represents an underestimate, since some **bee sting** deaths are erroneously attributed to heart attacks, sun stroke and other causes. The impacts of **bee stings** can differ widely. Aug 13, 2015

Use of honey and other bee products in human treatments traced back thousands of years. Apitherapy include bee venom. Whereas bee venom therapy is to treat various diseases such as arthritis, rheumatoid arthritis, multiple sclerosis (MS), lupus, sciatica, low back pain, and tennis elbow to name a few. Bee venom contains at least 18 pharmacologically active components including various enzymes, peptides and amines. Sulfur is believed to be the main element in inducing the release of cortisol from the adrenal glands and in protecting the body from infections. Contact with bee venom produces a complex cascade of reactions in the human body. The bee venom is safe for human treatments, the median lethal dose (LD50) for an adult human is 2.8 mg of venom per kg of body weight. However, most human deaths result from one or few bee stings due to allergic reactions, heart failure or suffocation from swelling around the neck or the mouth. As compare with other human diseases, accidents and other unusual cases, the bee venom is very safe for human treatments.

Treatment of Hypersensitivity

The preferred first line of action to scrape off the bee stingers carefully (by avoiding to pull or squeeze the stingers, which could lead to injection of more venom), although this action is mainly relevant if performed within 60 s of the stinging event, in which period the stinger ejects all its venom. Other studies state that the first-line of action should be to administer intramuscular adrenaline (also known as epinephrine), and only then remove the stinger. adrenaline plays a critical role in the mortality and morbidity for allergic patients. Adrenaline acts as an α and β-agonist. Through its α-1 agonistic effect, it works as a vasoconstrictor, which prevents and relieves airway edema, hypotension, and shock. The β-1 agonistic effects of adrenaline are chronotropic and inotropic and thus increase the rate and force of cardiac contractions, while the β-2 agonistic effects of adrenaline lead to bronchodilation.

Therapy Against Massive Bee Envenoming

The ideal treatment against the severe toxic effects of bee venom would likely be antivenom. However, there are no specific antivenoms available, although major efforts are being made. Clinical monitoring should focus on levels of creatinine, serum urea nitrogen, electrolytes, and myoglobin to asses renal function and the risk of rhabdomyolysis. Furthermore, to check for the development of acute respiratory distress

syndrome and acidosis, blood pH, and oxygen levels should be monitored. If a patient shows signs of myoglobinuria, intravenous injection of sodium bicarbonate can be performed for alkalization of urine (i.e., to accelerate renal excretion). Alkaline diuresis can prevent the crystallization of myoglobin in kidney tubules, which may eventually lead to acute renal failure. Additionally, aggressive hydration and diuretics are often administered. The patient can be started on either hemo or peritoneal dialysis, exchange transfusion, or plasmapheresis, to eliminate low molecular weight components of the venom, such as melittin or PLA2, or if acute renal failure develops.

https://www.cnet.com/pictures/the-most-venomous-animals-on-earth-ranked/32/

- Top 10 Most Poisonous Animals

https://onekindplanet.org/top-10/top-10-most-poisonous-animals/

- The Most Poisonous/Venomous Animals in the World

https://sciencebasedlife.wordpress.com/2011/04/12/the-most-poisonousvenomous-animals-in-the-world/

POISONOUS PLANTS

1. Castor Bean:

The castor bean plant (*Ricinus communes*) is grown for commercial and ornamental purposes. The residue or pomace after castor oil extraction of castor beans gives rise to dust that may cause sensitivity reactions or poisoning. Ingestion of only one castor been has apparently caused fatal poisoning when the bean was thoroughly chewed. If the beans are swallowed whole, poisoning is unlikely because the hard seed coat prevents rapid absorption. *Ricin*, a toxic albumin found in castor beans, contains two polypeptide chains held together by a single disulfide bond. Chain B is a lectin that binds to the surface of the cell to facilitate toxin entry into the cell. Chain A disrupts protein synthesis by activating the 60S ribosomal subunit. The pulp of the seed contains allergenic glycoproteins, which cause allergic dermatitis, rhinitis and asthma in sensitized industrial workers.

Toxic manifestations:

The principal manifestations of poisoning with castor beans are vomiting, diarrhea and circulatory collapse. Ingestion of castor beans causes burning of the mouth, nausea, vomiting, diarrhea, abdominal pain, drowsiness, cyanosis, stupor, circulatory collapse, retinal haemorrhage, haematuria and convulsions. The vomitus and stools may contain blood. Chronic poisoning causes dermatitis and inflammation of the nose, throat and eyes. The lethal dose of ricin in man has been estimated to be 1 mg/kg body weight (about eight seeds).

Treatment:

- Gastric decontamination with syrup of ipecac (unless vomiting has already occurred), gastric lavage, and/or activated charcoal should be considered to prevent absorption of toxin.
- Whole bowel irrigation has been suggested to decrease transit time of the seeds.
- Maintain circulation by blood transfusions.
- Control convulsion with diazepam.
- Little amount of ricin is excreted in the urine; therefore forced diuresis is not indicated.

- No specific antidote exists and the majority of patients have an excellent outcome.

2. Mushrooms:

Poisonous mushrooms may grow wherever nonpoisonous mushrooms grow. The most dangerous species are *Amanita phalloides, Amanita verna, Amanita virosa, Gyromitra esculenta* and the *Galerina species*. Ingestion of part of one muschroom of a dangerous species may be sufficient to cause death. Over 100 fatalities occur each year from eating poisonous mushrooms. *Amanita phalloides* is the most toxic species and contains a number of cyclopeptides, of which amatoxins (cyclic octapeptides), phallotoxins (cyclic heptapeptides) and virotoxins (cyclic heptapeptides) are responsible for human poisoning following ingestion. Of the amatoxins, α-amanitin is the chief component and, together with β-amanitin, probably produces the hepatorenal syndrome seen with mushroom ingestions. Amatoxins are potent inhibitors of cellular protein synthesis. They inhibit RNA polymerase II within the nucleoplasm at very low concentrations and thus interfere with both RNA and DNA transcription. Those cells with the highest replication rates and most direct contact with the amatoxins (e.g. liver, kidney and intestinal cells) develop necrosis. Other mushrooms of the *Amanita genus* as well as of the genus *Galerina* may cause similar poisoning. Some mushrooms (e.g. *Inocybe fasigiata* and *Clitocybe cerrusata*) contain the alkaloid muscarine, which produces the same effect as parasympathetic stimulation on smooth muscles and glands. *Amanita muscaria* contains the isoxazole derivative ibotenic acid and muscimol, its decarboxylated metabolite. Ibotenic acid, which is structurally similar to the stimulatory neurotransmitter glutamic acid, is decarboxylated *in vivo* to muscimol. The stereochemistry of muscimol is very similar to that of the depressant neurotransmitter gamma aminobutyric acid (GABA) and may stimulate GABA, with typical GABA manifestations. Gyromitrin is the most toxicologically important of the nine hydrazones isolated from *Gyromitra esculenta*. Structurally, gyromitrin is an aldehyde that hydrolyzes in the body to N-monomethylhydrazine. The hydrazine moiety reacts with pyridoxine, resulting in inhibition of pyridoxal phosphate-related enzymatic reaction. This interference with pyridoxal phosphate disrupts the function of GABA as an inhibitory neurotransmitter.

Signs and Symptoms:

a- ***Cyclopeptide-containing mushrooms: e.g.*** *Amanita phalloides and Galerina autumnalis*. After a latent interval of 6-24 hours, severe nausea and vomiting begin and progress variably to diarrhea, bloody vomitus and stools, painful tenderness and enlargement of the liver, oliguria or anuria, jaundice, pulmonary oedema, headache, mental confusion and depression, hypoglycaemia and signs of cerebral injury with coma or convulsion. The fatality rate is about 50%.

b- ***Monomethyl hydrazine-containing mushrooms:*** *e.g. Gyromita ambigua and Gyromita esculenta*. Symptoms may include dizziness, fatigue, nausea, vomiting, severe headache and abdominal pain. Most gyromitrin ingestions result in mild symptoms, however, seizures, coma and death have been reported in severe cases. The fatality rate is 15-40%.

c- ***Muscarine-containing muschroosms:*** *e.g. Inocybe and Clitocybe species*. Typically, symptoms begin within 15 minutes to 1 hour with headache, vomiting, diarrhea, bradycardia, hypotension, salivation, miosis, bronchospasm and lacrimation. Cardiac arrhythmia may occur. The fatality rate is 5%.

d- ***Ibotenic acid and muscimol-containing mushrooms:*** *e.g. Amanita muscaria and Amanita pantherina.* Intoxication usually occurs 30 minutes after ingesting these mushrooms and is marked by hyperactivity, ataxia, euphoria, hallucinations, anxiety, agitation and tremors. Delirium, psychosis, coma, myoclonic movements and convulsions may be seen with severe poisonings. This excitatory period typically lasting about 3 hours is followed by a 10-15 hour period of exhaustion and somnolence. Fatalities are rare.

Treatment:

a- **Emergency measures:** Remove ingested muschrooms by ipecac emesis unless the patient has already vomited. After emesis, give activated charcoal in 70% sorbitol to aid in the removal of any unabsorbed poison.

b- **Antidotes:** A variety of drugs including the silymarin group, penicillin G, thioctic acid and vitamin C have been suggested for the treatment of *Amanita* poisoning. Penicillin G and silymarin are thought to inhibit amatoxin uptake by

hepatocytes. Silymarin stimulates RNA polymerase and scavenge free radicals. Thioctic acid (coenzyme of the Krebs cycle) was beneficial in a small series of poisoning. Its mechanism of action is unclear. For gyromitrin poisoning, give pyroidoxine, 25 mg/kg intravenously. For muschrooms producing predominantly muscarinic-cholinergic symptoms, give atropine, 1 mg orally or subcutaneously. For cardiac arrhythmias resulting from *Clitocybe* ingestion, propranolol may be useful. For the excitatory effects of *Amanita pantherina*, diazepam may be useful.

c- General measures:

- Careful control of fluid and electrolyte balance must be continued for 10-15 days.
- Repeated haemodialysis or charcoal haemoperfusion has been successfully in bringing about complete recovery in cases of *Amanita phalloides* poisoning.
- Large quantities of carbohydrate appear to help protect the liver from further damage.
- Give vitamin K for bleeding.

Toxicity of salicylate:

These compounds are derivatives of salicylic acid and include acetyl salicylic acid (ASA or aspirin), sodium salicylate, and methyl salicylate.

Salicylates are commonly used and available without prescription. Aspirin is now rarely used as an anti-inflammatory medication and will be reviewed only in terms of its antiplatelet effects (doses of 81 mg once daily), methyl salicylate (oil of wintergreen) is so irritating that it can only be used as an external application.

Salicylates for therapeutic use are available as tablets, capsules, powders, effervescent tablets and liquid preparations for ingestion; rectal suppositories; and as liniments, creams and lotions for topical application.

Uses of salicylate

1. Sodium salicylate and acetyl salicylic acid:

a. Antipyretic.

b. Analgesic.

c. Treatment of rheumatoid arthritis.

d. Low-dose aspirin is used in the prophylaxis of cerebrovascular ischemic events, angina pectoris, it is recommended for the prevention of colon cancer, and migraine. Accumulating data suggests that aspirin may prevent or protect against the development of colon and possibly other types of gastrointestinal cancers.

N.B: Combination of warfarin with aspirin may improve efficacy in preventing ischemic heart disease, but it may increase the chances of a hemorrhagic fatal stroke.
N.B: The antiplatelet action of aspirin contraindicates its use by patients with hemophilia.

2. Sodium amino salicylate:

It is used sometimes as a second-line drug in the management of tuberculosis.

3. Bismuth subsalicylate:

It is used to treat diarrhea, and as prophylaxis for travelers' diarrhea.

4. New derivatives of salicylic acid:

a. **Mesalamine** (5-aminosalicylic acid) is used in the treatment of inflammatory bowel disease.

b. **Olsalazine** (sodium azodisalicylate) used in relieving manifestations of ulcerative colitis, **Sulfasalazine** (salicylazosulfapyridine) is also beneficial.

c. **Diflunisal**, a difluorophenyl derivative of salicylic acid is said to be much more potent than aspirin in the treatment of musculoskeletal sprains and osteoarthritis.

d. **Benorylate** (4-acetamidophenyl-o-acetylsalicylate) is an ester of aspirin and paracetamol. It causes less gastric irritation and bleeding.

The usual therapeutic dose in adults is 4 gm/day. Toxicity can result if this is exceeded. Manifestations are a combination of those seen in aspirin and paracetamol poisoning with particular tendency toward centrilobular hepatic necrosis.

5. Locally acting salicylates:

a. **Salicylic acid** is a keratolytic agent.

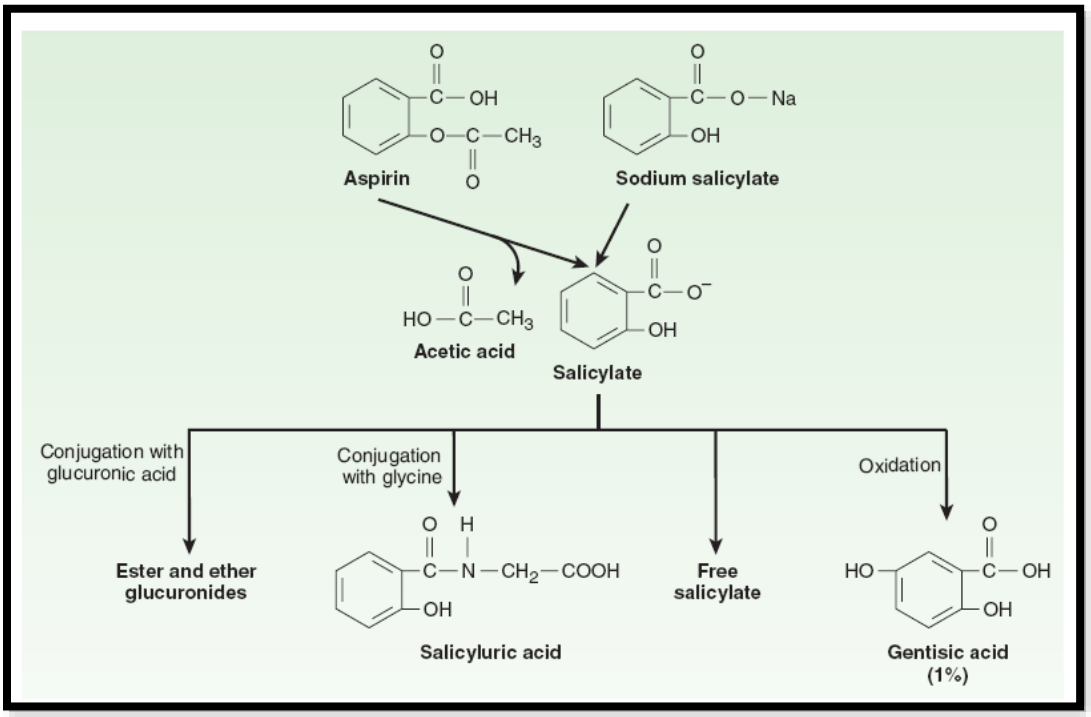
b. **Methyl salicylate** (oil of wintergreen), is used for the local treatment of musculoskeletal pain and inflammation.

N.B: one teaspoonful of oil of wintergreen (5 ml) is equivalent to approximately 7000 mg of salicylate or 21.7 adult aspirin tablets.

c. **Homomenthyl salicylate** (homosalate) is a sunscreen agent found in many sunscreen products and contains 46% salicylic acid.

Kinetics of salicylate

Salicylic acid is a simple organic acid with a pKa of 3.0. Aspirin (acetylsalicylic acid; ASA) has a pKa of 3.5. After oral administration aspirin is rapidly deacetylated by esterases in the body to produce salicylate. Unionized salicylates are passively absorbed mainly from the upper small intestine. Salicylates (except for diflunisal) cross both the blood–brain barrier and the placenta and are absorbed through intact skin (especially methyl salicylate). Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in first-order elimination and a serum half-life of 3.5 hours. At anti-inflammatory dosages of aspirin (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, leading to a half-life of 15 hours or more.



Structure and metabolism of the salicylates.

Mode of Action

- Salicylates stimulate the respiratory center in the brainstem leading to hyperventilation and respiratory alkalosis. They also interfere with Krebs cycle, inhibit production of ATP, and increase lactate production, leading to ketosis and a wide anion-gap metabolic acidosis.

- In children, respiratory alkalosis is quite transient, and metabolic acidosis is the predominant feature. Respiratory acidosis in salicylate overdose indicates grave prognosis and is seen in salicylate induced pulmonary edema, CNS depression from mixed overdose, or severe fatigue due to prolonged hyperventilation.

- Salicylates are extremely irritating to the GI mucosa, and overdose often results in hemorrhagic gastritis.
- Aspirin is commonly involved in allergic reactions, ranging in severity from urticaria or angioedema to acute anaphylaxis.

Clinical (Toxic) Features

1. Acute Poisoning:

a. **Early**—Nausea, vomiting, sweating, tinnitus, vertigo, and hyperventilation due to respiratory alkalosis. Irritability, confusion, disorientation, hyperactivity, slurred speech, agitation, combativeness, hallucinations, ataxia, and restlessness may be early findings in patients with severe toxicity.

b. **Late**—Deafness, hyperactivity, agitation, delirium, convulsions, hallucinations, hyperpyrexia. Coma is unusual.

c. **Complications**—Metabolic acidosis, pulmonary edema, rhabdomyolysis, cardiac depression, thrombocytopenic purpura. Gastrointestinal bleeding, Dehydration and

hypokalemia, QT prolongation are common complications. perforation and pancreatitis are less common complications.

N.B:

Salicylates must **not** be therapeutically administered to children under 19 years of age, especially if they are suffering from chicken pox or influenza. There is a serious risk of precipitating Reye's syndrome which can be fatal.

Reye's Syndrome (Stage Manifestations)

I Lethargic
II Stuporous, sluggish pupillary reaction, conjugate deviation of eyes (oculocephalic reflex)
III Comatose, decorticate posture, sluggish pupillary reaction, conjugate deviation of eyes (oculocephalic reflex)
IV Comatose, decerebrate posture, sluggish pupillary reaction, inconsistent response (oculocephalic reflex)
V Comatose, flaccid posture, no pupillary reaction, no response to painful stimuli, no response to oculocephalic reflex

Treatment of Reye's syndrome:

a. Admit the patient to an intensive care unit.

b. Raise the head-end of bed.

c. Mannitol IV (0.2 to 1.0 gm/kg).

d. Acute hyperventilation may be helpful.

e. Short acting barbiturates in resistant cases.

Chronic Poisoning (Salicylism):

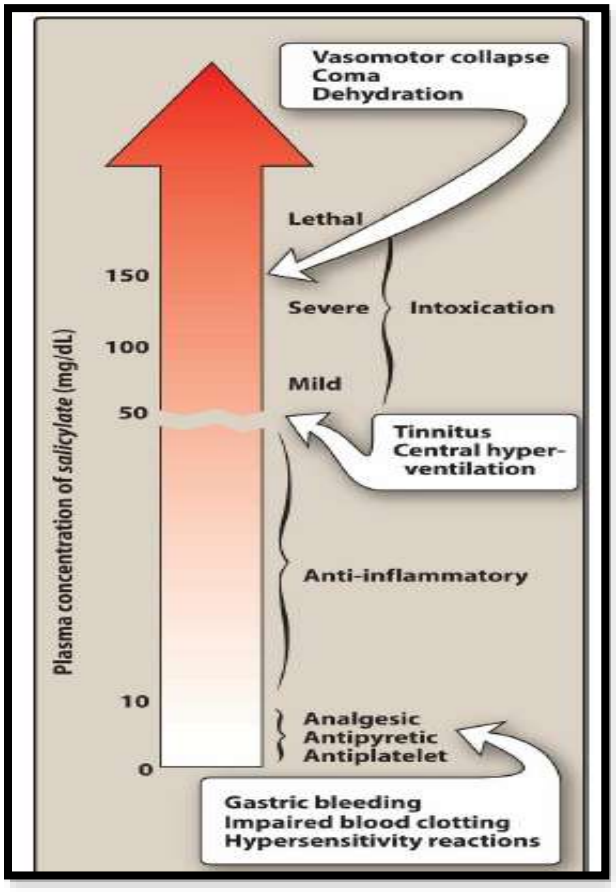
a. This is characterized by slow onset of confusion, agitation, lethargy, disorientation, slurred speech, hallucinations, convulsions, and coma. There may also be tinnitus, hearing loss, nausea, dyspnea, tachycardia and fever.

b. Sometimes "salicylism" presents as pseudo sepsis syndrome characterized by fever, leukocytosis, hypotension, and multi-organ system failure and acute renal failure.

c. Prolongation of PT and PTT, thrombocytopenia.

d. Chronic maternal ingestion is associated with an increased incidence of stillbirths, antepartum/postpartum bleeding, prolonged pregnancy/labour, and lower birth weight.

Note: Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy.



Management of salicylate toxicity

- Immediate management includes estimation of arterial blood gases, electrolytes, renal function, blood glucose (hypoglycemia is particularly common in children) and plasma **salicylate** concentration.
- The patient is usually dehydrated and requires intravenous fluids.
- A stomach washout is performed, if within one hour of ingestion.
- Activated charcoal (AC) should be administered. Multiple dose activated charcoal is advised until the **salicylate** level has peaked. each gram of AC can adsorb 550 mg of the drug. A 10:1 ratio of AC to salicylate ingested appears to result in maximum efficiency.
- Blood gases and arterial pH normally reveal a mixed metabolic acidosis and respiratory alkalosis. Respiratory alkalosis frequently predominates and is due to direct stimulation of the respiratory center. The metabolic acidosis is due to uncoupling of oxidative phosphorylation and consequent lactic acidosis. If acidosis predominates, the prognosis is poor.
- Absorption may be delayed and the plasma **salicylate** concentration can increase over many hours after ingestion. Depending on the **salicylate** concentration and the patient's clinical condition, an alkaline diuresis should be commenced using intravenous sodium bicarbonate. However, this is potentially hazardous, especially in the elderly. So, sodium bicarbonate is given to alkalinize the urine and promote salicylate excretion by trapping the salicylate in its ionized, polar form.

Urinary alkalinization regimen for aspirin

Indicated in adults with a salicylate level in the range 600–800 mg/L and in elderly adults and children with levels in the range 450–750 mg/L

Adults:

For mild poisoning: 1 L of 1.26% sodium bicarbonate (isotonic) + 40 mmol KCl is added to the first bottle of 5% dextrose and is taken IV over 4 h, If alkalinization (i.e. urinary pH between 7.5 and 8.5) is not achieved in a few hours, it can be repeated.

For severe poisoning: 50-mL i.v. boluses of 8.5% sodium bicarbonate (note: additional KCl will be required)

Children: 1 mL/kg of 8.4% sodium bicarbonate (= 1 mmol/kg) + 20 mmol KCl diluted in 0.5 L of dextrose saline infused at 2–3 mL/kg/h

Note: Alkalinization should be stopped when serum salicylate level falls below 35 mg/100 ml.

Children metabolize **aspirin** less effectively than adults and are more likely to develop a metabolic acidosis and consequently are at higher risk of death.

Plasma electrolytes, **salicylate** and arterial blood gases and pH must be measured regularly. **Sodium bicarbonate** acutely lowers plasma potassium, by shifting potassium ions into cells. Supplemental intravenous potassium may cause dangerous hyperkalaemia if renal function is impaired, so frequent monitoring of serum electrolytes is essential.

If the **salicylate** concentration reaches 800–1000 mg/L, hemodialysis is likely to be necessary to remove the salicylate more quickly and restore acid-base balance and fluid status. So, hemodialysis may also be life-saving at lower **salicylate** concentrations if the patient's metabolic and clinical condition deteriorates.

Supportive measures:

1. Correct dehydration with 0.9% saline 10 to 20 ml/kg/ hr over 1 to 2 hours until a good urine flow is obtained (at least 3 to 6 ml/kg/hr).

2. Hypoprothrombinaemia can be corrected by 2.5 to 5 mg of vitamin K IV every day.

3. Hyperpyrexia must be tackled by cooling measures (e.g. ice in the axilla and groin).

4. Correction of metabolic acidosis with NaHCO3.

5. Correction of hypocalcaemia with calcium gluconate IV (5 to 10 ml in adults).

6. Correct hypokalaemia as needed. Patients undergoing forced or alkaline diuresis may require large amounts of potassium supplementation due to renal potassium wasting.

7. Correction of hypoglycaemia with glucose IV (50 ml of 5% dextrose or 1 ml/kg).

8. Treatment of convulsions with benzodiazepines.

9. Mild cerebral oedema and elevated intracranial pressure (ICP) can be managed by head elevation and administration of mannitol

10. Salicylates can interfere with coagulation mechanisms, therefore, patients with evidence of active bleeding or coagulation disorders require laboratory monitoring to include prothrombin time (PT) and INR. Give blood or blood products (fresh frozen plasma) if bleeding is excessive. Vitamin K may be beneficial in the presence of a prolonged PT or INR.

Paracetamol (Acetaminophen)

Pharmacokinetics

Acetaminophen is rapidly absorbed from the GI tract and undergoes significant first-pass metabolism. It is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of acetaminophen is hydroxylated to form N-acetyl-p-benzoquinoneimine, or NAPQI, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage. At normal doses of acetaminophen, NAPQI reacts with the sulfhydryl group of glutathione produced by the liver, forming a nontoxic substance. Acetaminophen and its metabolites are excreted in urine.

Acetaminophen toxicity

Acetaminophen is one of the drugs 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. Normally acetaminophen is a safe drug because glutathione produced by the liver combines with NAPQ to detoxify it so, at normal therapeutic doses, acetaminophen has few significant adverse effects.

With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins. Hepatic necrosis, a serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of acetaminophen-induced hepatotoxicity. Acetaminophen should be avoided in patients with severe hepatic impairment.

N.B:

• Alcohol is a powerful inducer of microsomal enzymes. It increases the production of NAPQ from acetaminophen resulting in toxicity, this effect occurs also with other CYP-450 enzyme inducers.

There are four phases typically describing acetaminophen toxicity. The antidote for acetaminophen toxicity, N-acetylcysteine (NAC), works as a glutathione precursor and glutathione substitute, and assists with sulfation. NAC may also function as an antioxidant to aid in recovery. NAC is most effective when initiated within 8 to 10 hours of ingestion. The Rumack-Matthew nomogram, which is based on the time of ingestion and the serum acetaminophen level, is utilized after an acute ingestion to determine if NAC therapy is needed. The nomogram is helpful to predict acetaminophen toxicity when levels can be obtained between 4 and 24 hours post ingestion.

Acetaminophen toxicity can be decreased by providing sulfhydryl donors like N-acetylcysteine (antidote of choice). Acetaminophen overdose constitutes medical emergency and 90% of patients will develop severe liver damage. The severity of poisoning is estimated from a serum acetaminophen concentration measurement, if plasma concentration is **greater than 300 μg/ml at 4 hours or 45 μg/ml at 15 hours after ingestion.** Gastric lavage (with activated charcoal) should be done to prevent further absorption but it is **ineffective after 4 hours** of ingestion.

Phase I:

Occurs within few hours after ingestion (0-24 hours): loss of appetite, nausea, vomiting, general malaise.

Phase II:

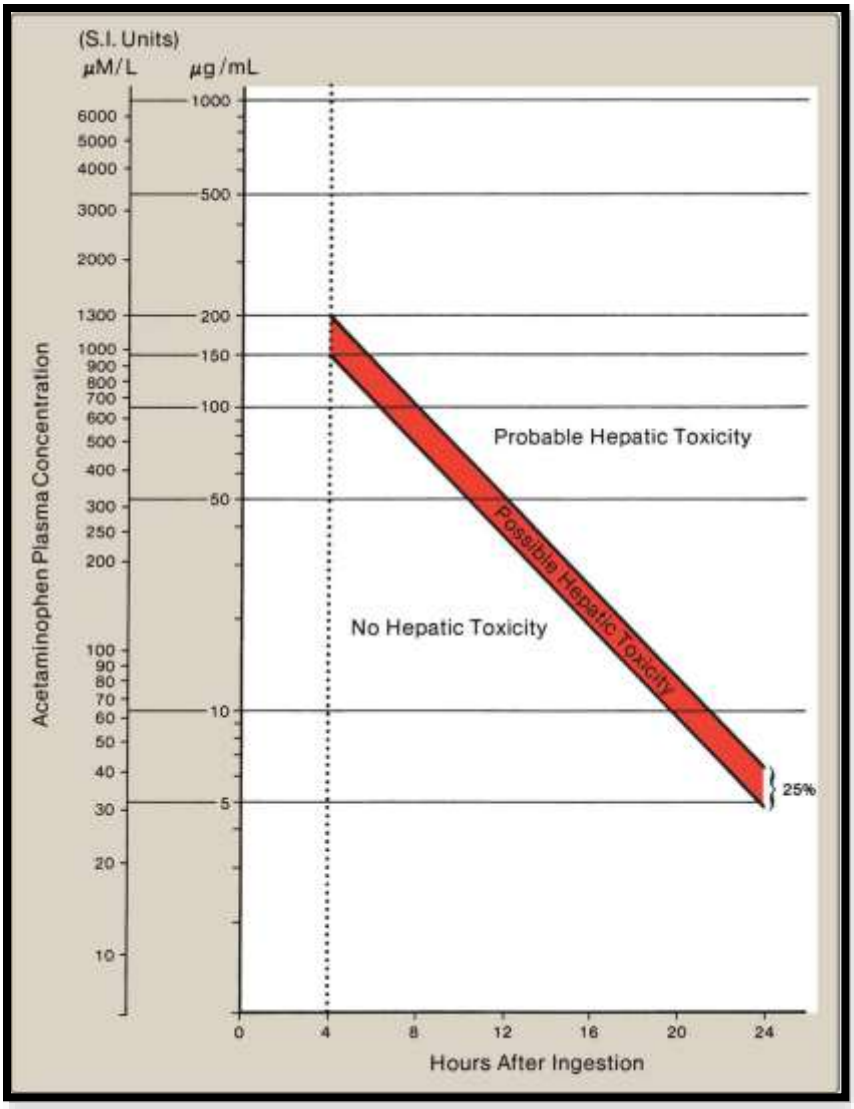
Occurs within 24-72 hours after ingestion: abdominal pain, increase in serum liver enzymes.

Phase III:

occurs within 72-96 hours post ingestion: liver necrosis, jaundice, encephalopathy, renal failure, death

Phase IV:

occurs within (> 4 days to 2 weeks) complete resolution of symptoms and organ failure.



Rumack-Matthew nomogram for acetaminophen poisoning. Acetaminophen concentration plotted vs. time after exposure to predict potential toxicity and antidote use.

Management of paracetamol toxicity

If a potentially toxic overdose is suspected, the stomach should be emptied if within one hour of ingestion. The antidote should be administered and blood taken for determination of **paracetamol** concentration, prothrombin time (INR), creatinine and liver enzymes. The decision to stop or continue the antidote can be made at a later time.

Intravenous **acetylcysteine** and/or oral **methionine** are potentially life-saving antidotes and are most effective if given within eight hours of ingestion; benefit is obtained up to 24 hours after ingestion. For serious **paracetamol** overdoses seen greater than 24 hours after ingestion, advice should be sought from poisons or liver specialists. **Acetylcysteine** is administered as an intravenous infusion. In approximately 5% of patients, pseudo allergic reactions occur, which are usually mild. If hypotension or wheezing occurs, it is recommended that the infusion be stopped and an antihistamine administered parenterally. If the reaction has completely resolved, **acetylcysteine** may be restarted at a lower infusion rate. Alternatively, **methionine** may be used

Methionine is an effective oral antidote in **paracetamol** poisoning. It may be useful in remote areas where there will be a delay in reaching hospital or when **acetylcysteine** is contraindicated.

Corrosives

Corrosive is defined as any substance that cause destruction by chemical action when contact with living tissue. Corrosive may be acids or alkali.

Acids as: strong acids any substance with a PH below 2 it includes:

- organic acids as (oxalic, acetic, tartaric acids)
- Inorganic acids as: (sulfuric, hydrochloric, nitric, phosphoric acids)0-

All acids produce tissue damage but they differ in intensity of that damage.

Mechanism of toxicity:

Acids denature tissue protein. The resulting lesion will cause cell death that appeared as coagulative necrosis lead to formation of tough leathery scab that delay further corrosive damage and reduce systemic absorption so, damage is often limited to the site of injury either skin or GI tract.

Clinical Features of toxicity

After corrosives ingestion:

- Burning pain from the mouth to the stomach.
- Abdominal pain is often severe.
- Intense thirst. However, attempts at drinking water usually provoke retching.
- The vomitus is brownish or blackish in color due to altered blood (coffee grounds vomit), and may contain shreds of the charred wall of the stomach.
- Features of generalized shock are usually apparent.
- exposure to acids may produce metabolic acidosis, particularly following ingestion.

After corrosives Inhalation

If there is coincidental damage to the larynx during swallowing or due to regurgitation, there may be dysphonia, dysphagia, dyspnea. bronchial irritation and pulmonary edema.

After corrosives dermal contact:

- Contact with the eyes can cause severe injury including conjunctivitis, periorbital edema, corneal edema and Ulceration.
- Contact with skin cause staining of skin and burning.

Management of acid poisoning:

1.Respiratory distress due to laryngeal edema should be treated with 100% oxygen

2. administration of water or milk if the patient is seen within 30 minutes of ingestion (120–240 ml in an adult, 60–120 ml in a child). But no attempt must be made at neutralization with alkalis, since the resulting exothermic reaction can cause more harm than benefit. also, administration of buffering agents such as antacids can produce significant exothermic reaction.

3. Remove all contaminated clothes and jewelry then irrigate exposed skin copiously with saline. Non-adherent gauze and wrapping may be used. Deep second-degree burns may benefit from topical silver sulfadiazine.

4. Eye injury should be dealt with by retraction of eyelids and prolonged irrigation for at least 15 to 30 minutes with normal saline or lactated Ringer's solution, or tap water if nothing else is available.

5. gastric lavage first, the acid is suctioned out of the stomach completely to reduce risk of heat formation then cold water or milk is used as lavage fluid.

6. emesis must be avoided to prevent recurrent damage to the esophagus.

7. Administer antibiotics only if infection occurs.

Alkalis:

It is a chemical that have PH of 11.5. the degree of injury with alkali exposure depend on the concentration, quantity, length of exposure and type of alkali.

Clinical Features of toxicity

- The reaction of alkali in contact with tissues is saponification resulting in necrosis which don't destroy not only the epithelium but also the underlying mucosal wall, so systemic complications are common.

- Esophageal damage occurs within 3-5 days, intramucosal damage, inflammation, edema, cognition throughout the esophageal wall.

- Necrosis, inflammation, edema, esophageal ulceration, bleeding and perforation occur within 5-12 days

- Healing and scarring begin within 3-4 weeks.

Management of alkali poisoning

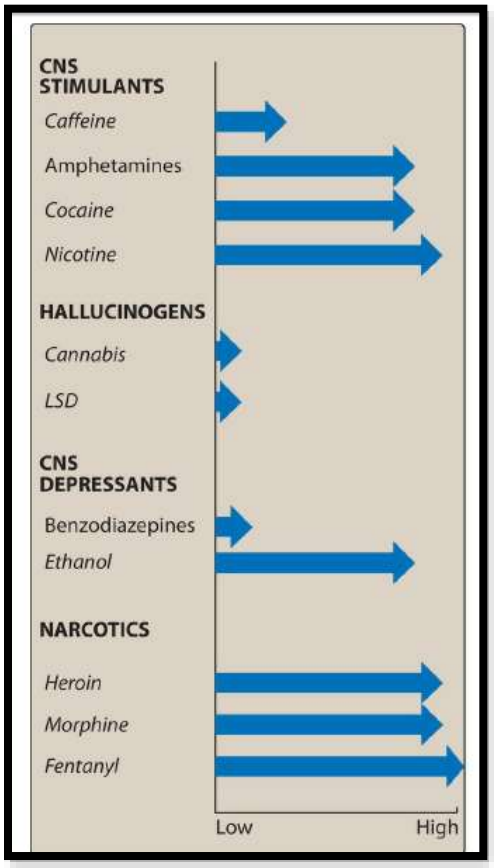
- Skin and eye contamination should be immediately flushed with water for at least 15-20 min. severe alkali burns should be irrigated for at least 8-24 hr. all contaminated clothing and jewelry should be removed.

- Gastric lavage.
- Milk or water is used to decrease damage to mouth, esophagus and stomach.
- Glucocorticoids is used to reduce fibrosis and esophageal rupture.
- Antibiotics is used to reduce further complications.

Substances of Dependence and Abuse

Drugs are abused (used in ways that are not medically approved) because they cause strong feelings of euphoria or alter perception. However, repetitive exposure induces widespread adaptive changes in the brain. As a consequence, drug use may become compulsive—the hallmark of addiction.

Every addictive drug causes its own characteristic spectrum of acute effects, but all have in common the characteristic that they induce strong feelings of euphoria and reward. With repetitive exposure, addictive drugs induce adaptive changes such as tolerance (ie, escalation of dose to maintain effect). Once the abused drug is no longer available, signs of withdrawal become apparent. A combination of such signs, referred to as the **withdrawal syndrome**



Relative potential for physical dependence of commonly abused substances

Sympathomimetics

Sympathomimetics are stimulants that mimic the sympathetic nervous system, producing “fight-or-flight” responses. Sympathomimetics usually produce a relative increase of adrenergic neurotransmitters at the site of action causing effects such as tachycardia, hypertension and hyperthermia. Many of these agents have a remarkable ability to produce pleasure.

Cocaine

It causes central nervous system (CNS) stimulation by inhibiting the reuptake of norepinephrine into the adrenergic neuron, thus increasing the availability of catecholamines at the synapse. The profound ability of cocaine to stimulate the pleasure center of the human brain is thought to result from inhibition of reuptake of dopamine and serotonin.

Cocaine has minimal bioavailability when taken by the oral route. Instead, the cocaine hydrochloride powder is snorted, or solubilized and injected. The cocaine powder cannot be effectively smoked, as it is destroyed upon heating. However, crack cocaine, an alkaloidal form, can be smoked. Smoking is an extremely effective route of administration, as the lungs are richly perfused with blood and carry the drug within seconds to its site of action, the brain. This causes an intense euphoria or “rush” positive reinforcement that is followed rapidly by an intense dysphoria or “crash” negative reinforcement.

The clinical manifestations of cocaine toxicity are a function of its stimulant effects.

Common reasons for cocaine users to present to the emergency department include:

- psychiatric complaints (depression precipitated by cocaine dysphoria, agitation/paranoia)
- convulsions which are a natural extension of the CNS stimulant effect
- Hyperthermia is caused by cocaine-induced CNS stimulation that increases heat production and vasoconstrictive effects of cocaine that minimize the ability to dissipate heat.
- chest pain can be chest muscle pain or cardiac in nature, as cocaine causes vasoconstriction of coronary arteries and accelerates the atherosclerotic process.

NOTE:

Commonly, cocaine is consumed with ethanol, which creates a secondary metabolite cocaethylene. The metabolite is cardiotoxic.

Cocaine toxicity is treated by calming and cooling the patient to manage hyperthermia as hyperthermia is one of the major causes of cocaine fatalities. Benzodiazepines, such as lorazepam, help to calm the agitated patient and can both treat and prevent convulsions. The remainder of cocaine toxicity is treated with short-acting antihypertensives, anticonvulsants, and symptomatic supportive care.

Amphetamine

- Amphetamine shows neurologic and clinical effects similar to those of cocaine.
- Dextroamphetamine is the major member of this class of compounds.
- Methamphetamine known as “speed” is a derivative of amphetamine.
- 3,4-**M**ethylene**d**ioxy**m**eth**a**mphetamine known as MDMA, or ecstasy or Molly) is a synthetic derivative of methamphetamine with both stimulant and hallucinogenic properties.

The effects of amphetamine may last longer and are associated with more stimulation and less euphoria when compared to cocaine. Treatment of amphetamine toxicity is similar to that of cocaine toxicity.

Lysergic acid diethylamide

LSD, lysergic acid diethylamide, is the most commonly recognized drug in the hallucinogen class. LSD produces its psychedelic effects through serving as a potent partial agonist at 5-HT2A receptors. The drug is also responsible for mood alterations, sleep disturbances, and anxiety. Repeated use rapidly produces tolerance through downregulation of serotonin receptors.

Although physical adverse effects are typically minimal, LSD may cause mydriasis, tachycardia, increased blood pressure and body temperature, dizziness, decreased appetite, and sweating. Perhaps, the most troubling side effects are the loss of judgment and impaired reasoning associated with use of LSD.

Marijuana

Cannabis is a plant that has been used by humans for over 10,000 years. the species Cannabis sativa is the plant most often used for its psychoactive properties. The main psychoactive alkaloid contained in marijuana is Δ9- tetrahydrocannabinol (THC). Specific receptors in the brain, cannabinoid or CB1 receptors are reactive to THC. When CB1 receptors are activated by marijuana, effects include physical relaxation, hyperphagia (increased appetite), increased heart rate, decreased muscle coordination, conjunctivitis, and minor pain control. Depending on the social situation, THC can produce euphoria, followed by drowsiness and relaxation.

The effects of marijuana on γ-aminobutyric acid (GABA) in the hippocampus diminish the capacity for short-term memory in users, mental activity, also THC decreases muscle strength and impairs highly skilled motor activity, such as that required to drive a car. The effects of THC appear immediately after smoking marijuana, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear.

In chronic marijuana users, tolerance develops rapidly, 9% of all users and will develop dependence, and withdrawal has been observed. Marijuana may be found in the body up to 3 months after last usage in heavy chronic users. For this reason, withdrawal occurs much later in individuals who previously used marijuana heavily. Withdrawal may include cravings, insomnia, depression, pain and irritability.

Although not well studied for medicinal use, marijuana has been used as an adjuvant in the treatment of chemotherapy-induced nausea and vomiting (CINV), cachexia secondary to cancer and AIDS, epilepsy, chronic pain, multiple sclerosis. Synthetic THC medications are available as prescription products and include **dronabinol** and **nabilone.** These medications are used for the prevention of CINV.

Morphine

Tolerance and physical dependence

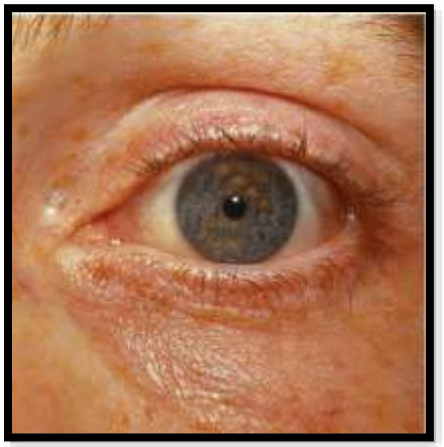
Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, emetic, and sedative effects of morphine. Tolerance usually does not develop to miosis (constriction of the pupils) or constipation.

Physical and psychological dependence can occur with morphine and other agonists. Withdrawal produces a series of autonomic, motor, and psychological responses that can be severe, although it is rare that withdrawal effects cause death.

A black box warning also has been included on the labeling of both opioids and benzodiazepines to alert prescribers of this dangerous combination as the depressant actions of morphine are enhanced by coadministration with CNS depressant medications.

Opioids + benzodiazepines = dangerous combination.

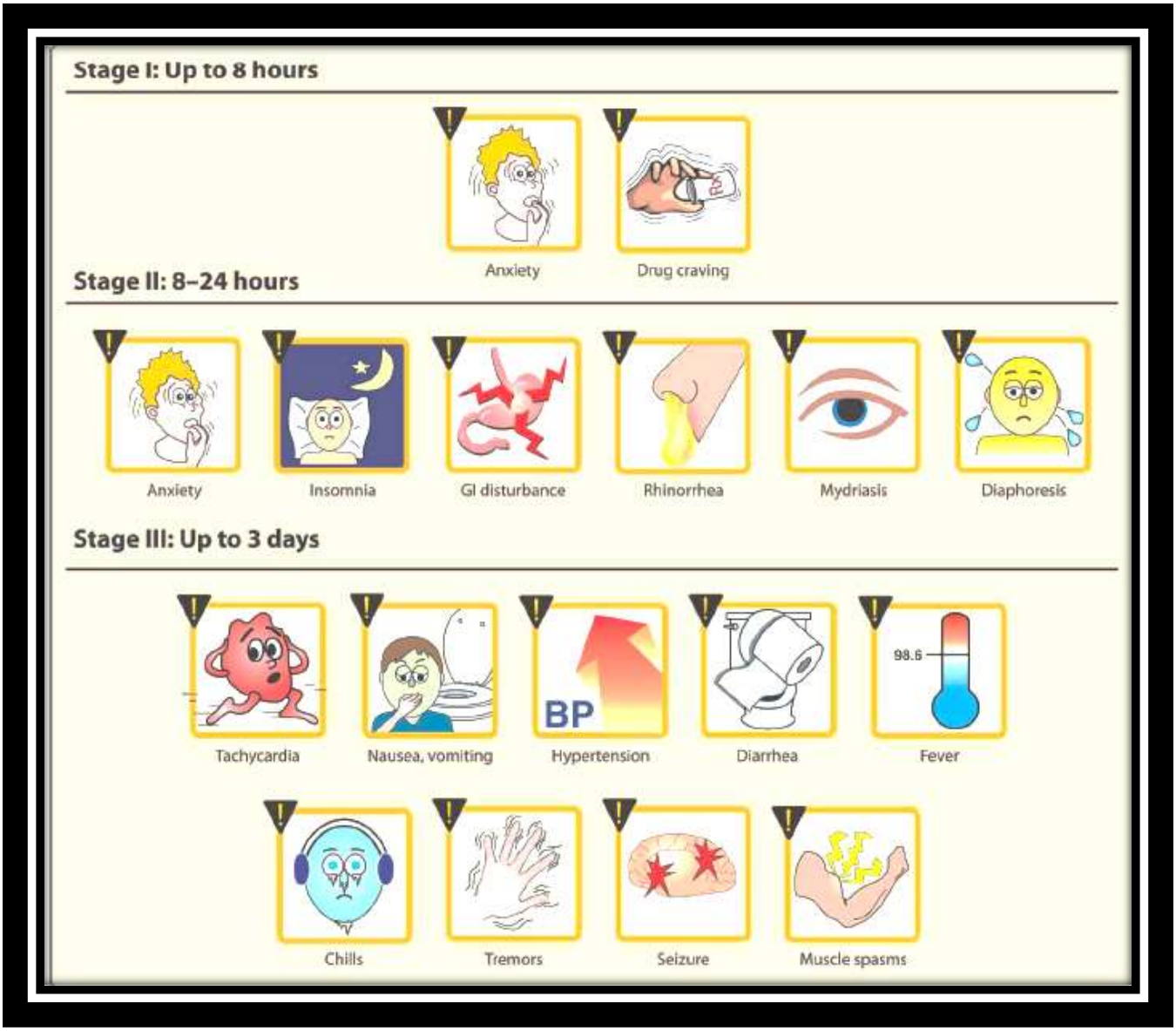
The pinpoint pupil (miosis) is characteristic of morphine use and here is little tolerance to this effect and considered a valuable sign in diagnosis of opioid poisoning.



Opiate withdrawal syndrome

The opioid antagonists bind with high affinity to opioid receptors, but they fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in individuals not taking opioids.

In opioid-dependent patients, antagonists rapidly reverse the effect of agonists, such as morphine or any full μ agonist, and precipitate the symptoms of opioid withdrawal.



Naloxone

Naloxone is a competitive antagonist at μ, κ, and δ receptors, with a 10-fold higher affinity for mu than for kappa receptors. It rapidly displaces all receptor-bound opioid molecules and, therefore, can reverse the effects of morphine overdose, such as respiratory depression and coma within 1 to 2 minutes of IV administration.

Naloxone can also be administered intramuscularly, subcutaneously, and intranasally, with a slightly longer onset of 2 to 5 minutes; however, little to no clinical effect is seen with oral naloxone due to extensive first-pass metabolism.

Note:

- Much higher doses and continuous administration of naloxone are needed to reverse the effects of buprenorphine due to its high affinity for the mu receptor.
- **Naloxone** is the **drug of choice for acute opioid poisoning** but it has to be repeated frequently.
- **Naloxone** is also used in **neonatal resuscitation** to reverse the effects of opioids (if used during labour). However, it should **not** be **used** for this purpose **if mother is dependent** on opioids. (Baby is also dependent in utero and naloxone can precipitate withdrawal).
- Naloxone is being added to opioids meant for oral use to minimize their addictive potential. If the patient takes the combination orally, only opioid is absorbed not naloxone. Thus, it will produce the desired action. However, if the person takes it by i.v. route for addiction, naloxone also reaches the blood and stops euphoria.

Naltrexone

Naltrexone has actions similar to those of naloxone, but it has a longer duration of action and can be given orally. For example, a single oral dose of naltrexone blocks the effect of injected heroin for up to 24 hours, and the intramuscular formulation blocks the effect for 30 days.

Naltrexone in combination with clonidine (and, sometimes, with buprenorphine) is used for rapid opioid detoxification. Naltrexone has been reported to cause hepatotoxicity and monitoring of hepatic function is recommended.

• **Naltrexone** is used as a **maintenance drug for opioid poisoning**. It is also used **to prevent relapse after opioid de-addition**. It is **also** used to **decrease craving** in chronic alcoholics.

Opioid De-addiction

- Chronic intake of opioids can result in physical and psychological dependence. If suddenly stopped, the person may develop severe withdrawal symptoms, which may be life threatening.
- For de-addiction of opioids (or any addictive drug), first aim is to stop the further use of the drug by the patient followed by maintenance of de-addiction (to prevent relapse).
- If addiction is of short duration and with small doses of addictive drug, sudden stoppage of drug therapy can be attempted and the mild withdrawal symptoms can be treated with β-blockers or clonidine.
- If addiction is of long duration or with large dose of opioids, sudden withdrawal of the offending drug may be dangerous (due to severe withdrawal symptoms). In such patients, the addictive drug is replaced by equivalent dose of methadone **(known as methadone maintenance)**. It prevents withdrawal symptoms by stimulating opioid receptors but is much less addictive. The dose of methadone is then gradually decreased and finally stopped.
- To prevent relapse after de-addiction, naltrexone is used. Naltrexone prevents euphoric action by blocking μ receptors. If the person again takes opioids (after deaddiction), there will be no euphoria and the person's resolution to quit addiction will be strengthened.

Summary:

- β-blockers and clonidine treat withdrawal symptoms.
- Methadone prevents withdrawal symptoms.
- Naltrexone is used to prevent relapse.
- Methadone is used as maintenance therapy in opioid dependence
- Naltrexone is used as maintenance therapy in opioid poisoning.

Nicotine

- Nicotine is an addictive substance, and physical dependence develops rapidly and can be severe.
- Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI upset often occurs. The transdermal patch and chewing gum containing nicotine have been shown to reduce nicotine withdrawal symptoms and to help smoker stop smoking.
- Bupropion, an antidepressant, can reduce the craving for cigarettes, assist in smoking cessation, and attenuate symptoms of withdrawal.

Varenicline

Varenicline is a partial agonist at neuronal nicotinic acetylcholine receptors in the CNS, so it produces less euphoric effects than nicotine (nicotine is a full agonist). Thus, it is useful as an adjunct in the management of smoking cessation in patients with nicotine withdrawal symptoms. Patients taking varenicline should be monitored for suicidal thoughts, nightmares and mood changes.

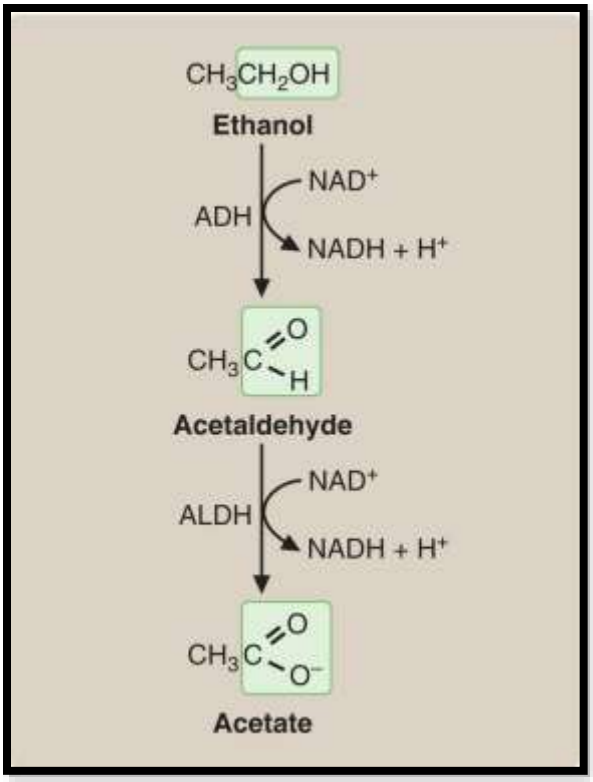
Ethanol

- Ethanol (or alcohol) is a clear colorless hydroxylated hydrocarbon that is the product of fermentation of fruits, grains, or vegetables. Ethanol consumption is a major cause of deadly automobile accidents, drownings, and fatal falls, and is a related factor in many hospital admissions. Ethanol is the most commonly abused substance in modern society.
- Alcoholism decreases life expectancy by 10 to 15 years, while Moderate consumption of alcohol (18-20 g daily, roughly equivalent to 50-100 ml of whiskey) decreases the risk of coronary artery disease by increasing HDL and decreasing LDL cholesterol. Drinking ethanol traditionally has been the most common route of administration, Peak ethanol levels are generally achieved in 20 minutes to 1 hour of ingestion.

- It is thought that ethanol exerts its desired and toxic effects through several mechanisms, including enhanced effects of the inhibitory neurotransmitter GABA, increased release of endogenous opioids, and altered levels of serotonin and dopamine.

- Ethanol is a selective CNS depressant at low doses, at high doses, it is a general CNS depressant, which can result in coma and respiratory depression.

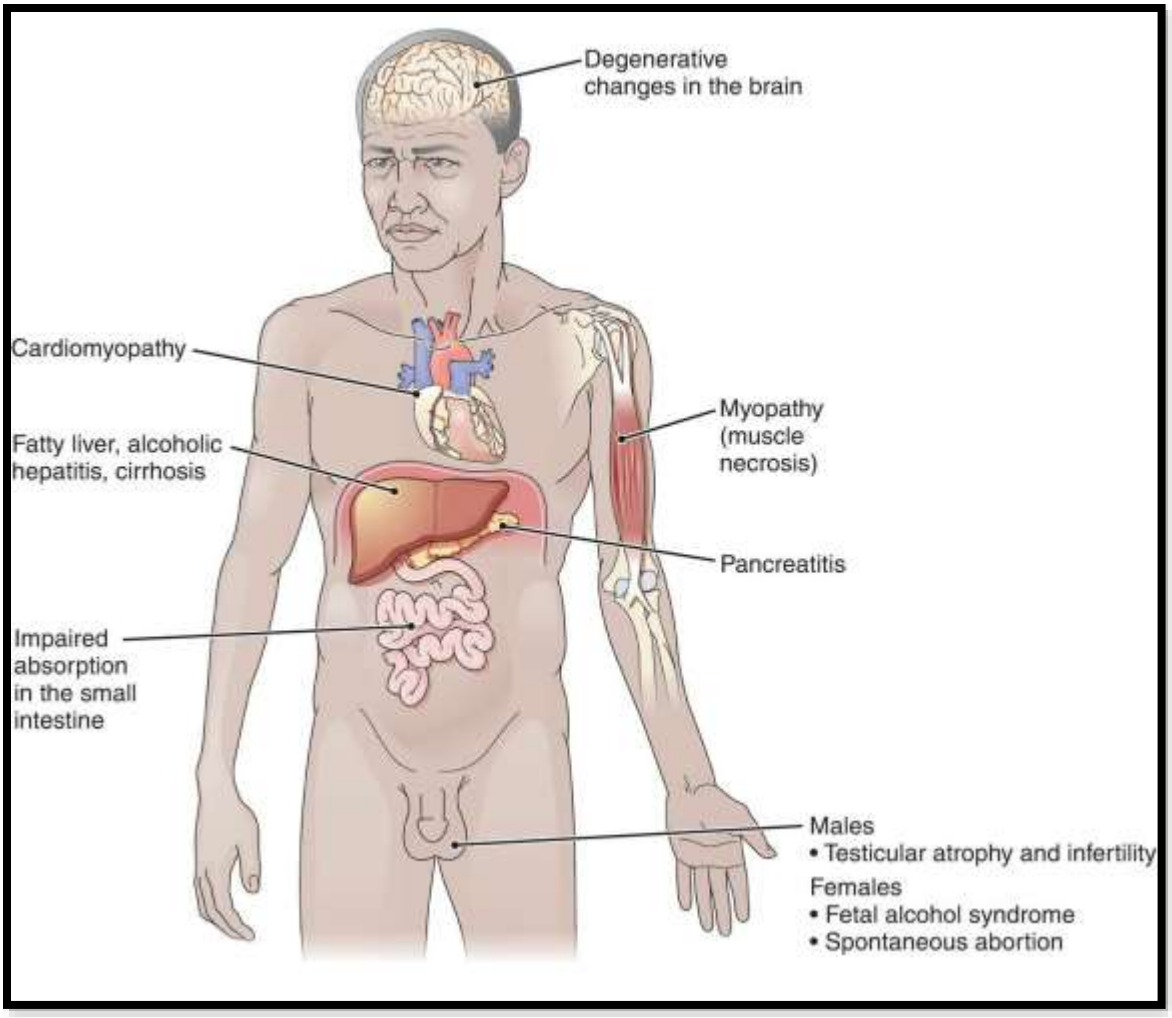
- Ethanol is metabolized by alcohol dehydrogenase to acetaldehyde and then by aldehyde dehydrogenase to acetate in the liver. It is metabolized by zero-order elimination at approximately 15 to 40 mg/dL/h. a breath sample can be used to determine blood alcohol levels.



- **Chronic ethanol abuse** can cause hepatic, cardiovascular, pulmonary, hematologic, endocrine, metabolic and CNS damage.

- **Chronic alcohol** consumption **induces microsomal enzymes**. More generation of toxic metabolite (NAPQI) of **acetaminophen** is responsible for increased risk of **hepatotoxicity** in alcoholics.

- Alcohol **increases** the chances of **hypoglycemia** in diabetic patients taking insulin and other oral hypoglycemic agents.



Treatment of Alcohol Dependence

- Sudden cessation of ethanol ingestion in a heavy drinker can precipitate withdrawal manifested by tachycardia, sweating, tremor, anxiety, agitation, hallucinations, and convulsions.
- Alcohol withdrawal is a life-threatening situation that should be medically managed with symptomatic/supportive care, benzodiazepines, and long-term addiction treatment. The following are drugs used in the treatment of alcohol dependence:

- **Benzodiazepines** (diazepam) are given to **prevent withdrawal**. These are long acting CNS depressants and can be withdrawn gradually.
- **Topiramate and ondansetron** can also decrease alcohol craving.

Disulfiram

Disulfiram blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase. This results in the accumulation of acetaldehyde in the blood lead to severe distressing symptoms known as disulfiram like reaction appears as flushing, tachycardia, hyperventilation, and nausea. Disulfiram has found some use in patients seriously desiring to stop alcohol ingestion to prevent the unpleasant effects of disulfiram-induced acetaldehyde accumulation.

Disulfiram like reaction is caused by:
- Chlorpropamide
- Cefoperazone
- Moxalactam
- Cefamandole
- Metronidazole
- Griseofulvin

Naltrexone

Naltrexone is a competitive and relatively long-acting opioid antagonist that helps decrease cravings for alcohol. It should be used in conjunction with supportive psychotherapy. Naltrexone is better tolerated than disulfiram and does not produce the aversive reaction that disulfiram does.

Acamprosate

Acamprosate is an agent used in alcohol dependence treatment programs and is thought to decrease cravings through its blocking effect on N-methyl-D-aspartate (NMDA)-mediated glutamatergic excitation. This agent should also be used in conjunction with supportive psychotherapy.

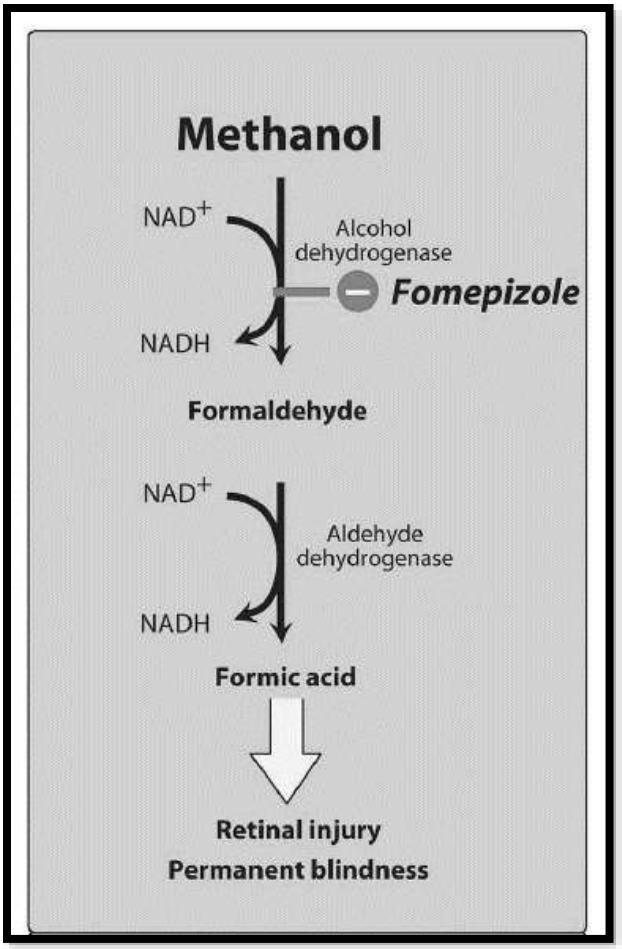
Drugs decreasing alcohol craving
None – **N**altrexone
Of – **O**ndansetron
The – **T**opiramate
Above – **A**camprosate

Methyl Alcohol (Methanol)

It is metabolized to formaldehyde (by alcohol dehydrogenase) and finally to formic acid (by aldehyde dehydrogenase). Accumulation of **formic acid** may **result in lactic acidosis (high anion gap metabolic acidosis), blindness and death. Specific toxicity of formic acid is retinal damage** leading to blindness.

Methanol poisoning can be treated by supportive measures, gastric lavage and sodium bicarbonate (to treat acidosis). **Ethanol** is useful because it **competitively inhibits the conversion of methanol to formic acid** by preventing the formation of toxic metabolites and allows the parent alcohols to be excreted by the kidney.

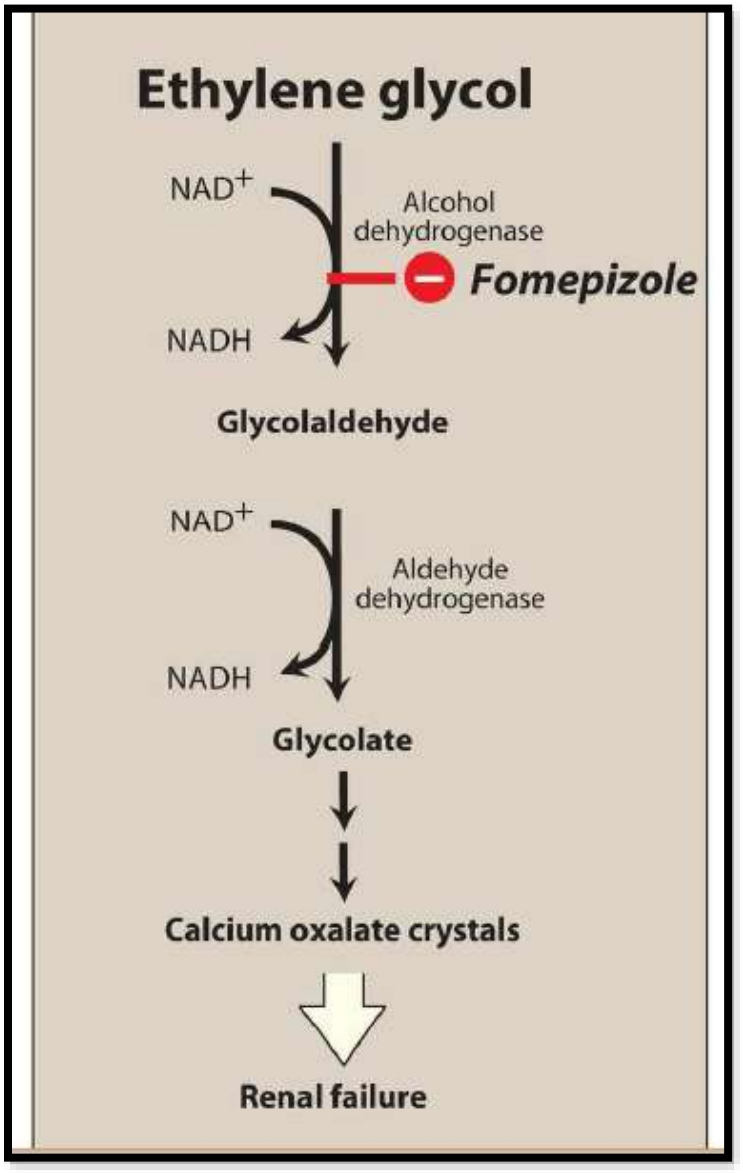
Hemodialysis is often utilized to remove the toxic acids that are already produced. **Fomepizole** can also be used in methanol poisoning because it is a **specific inhibitor of alcohol dehydrogenase**. In addition, cofactors are administered to encourage metabolism to nontoxic metabolites (**Folic acid or folinic acid)** can also be used because folate dependent systems are responsible for conversion of formic acid to CO_2.



Metabolism of methanol.

Ethylene glycol

Ethylene glycol is most commonly found in radiator antifreeze. ethylene glycol are oxidized to toxic products: glycolic, glyoxylic, and oxalic acids. Ethylene toxicity treated as methanol and cofactors are administered to encourage metabolism to nontoxic metabolites (thiamine and pyridoxine). Ethylene glycol ingestion may lead to renal failure, hypocalcemia, metabolic acidosis, and heart failure.



Metabolism of ethylene glycol.