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تنسيق بحوث

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Heavy metal poisoning

Arsenic

Sources of poisoning: the most inorganic trivalent arsenic compounds are arsenic trioxide, sodium arsenite and arsenic trichloride. Pentavalent inorganic compounds are arsenic pentoxide, arsenic acid and arsmates, such as lead arsenate and calcium arsenate.

Found: Arsenic is found in rocks and soils, foods, industry such as herbicides, fungicides and wood preservatives.Arsenic has been used as an assassination tool and homicidal agent because it is tastless, odorless and resembles sugar,

The routes of exposure to arsenic: inhalation, ingestion, skin. Arsenic is deposited in hair, nail and skin and can be detected in their tissues several years after chronic exposure. It crosses the placenta and can accumulate in the fetus.

Mechanism of toxicity:

Trivalent compounds of arsenic are principle toxic forms and pentavalent arsenic compunds have little effect on enzyme activity. Arsenic inhibits sulfhydryl enzymes causing disturbqnce in cell function. An example is the enzyme pyruvate dehydrogenase which is mecessary for oxidative decarboxylation of pyruvic acid to acetyl coA and co_2.

This enzyme inhibition hinders kerb,s cycle and cause accumulation of pyuvic acid leading to metabolic acidosis. It causes uncoupling of oxidative phosphorylation. Arsenic also initiates cellular oxidative processes leading to injury of multiple organs.

Signs and symptoms:

1-Gastrointestinal tract: irritation of mucosa of the GIT leads to burning sensation in the throat, esophagus and abdomen, nausea, vomiring with vomits often colored with blood or bile (vomits like ricewater, colic, diarrhea with watery and bloody stools and tenesmus.

2-Circulation: rapid and irregular pulse, dehydration and collapse.

3-Kidneys: nephritis, hematuria, proteinuria, oliguria and tubular necrosis

4-Hematologic: bone marrow depression resulting in anemia, thrombocytopenia or aplastic anemia.

5-Liver: fatty degeneration and necrosis followed by cirrhosis can be occur. Jaundice may develop in 1-2days.

6-Skin: cutaneous signs occur after systemic exposure. The hyperpigmentation is most pronounced on the eyelids, neck, nipples and groin

7-CNS: deliririum, seizures, coma and death.

8-Plumonary: pulmonary edema and respiratory failure.

Chronic poisoning

It is characterized by anorexia, Loss of weight, Garlic odor in breath, hyperpigmentation and Hyperkeratosis. There may be loss of hair (alopecia), deformation and loss of nails, corrosion of teeth, Peripheral neuritis, and Nephritis Liver damage. Long -term exposure to arsenic may cause caricinoma of skin and teratogenesis.

Treatment:

GI decontamination: gastric lavage should be considered if a recent life-threatening has occurred. Emesis is not recommended, as arsenic may cause seizures and coma within a short time. Activated charcoal dose not significantly absorbed arsenic. Urine should be alkalinizes to maintain a PH of 7 to prevent red cell breakdown products on renal tubules.

Antidotes: chelating agents such as **British antilewisite (BAL, dimercaprol)** bind to and enhance urinary eccretion of toxic metals. **D-penicillamine** is also used. **Dimeracaptosuccininc acid** (DMSA or succimet) is better than BAL. chelating agents are indicated in symptomatic patients and those with urine arsenic more than 200ug/L.

2) **Hemodialysis:** if renal failure occurs, hemodialysis should be considered along with chelation therapy.

3) **Supportive measures:** maintenance of fluid and electrolyte balance and tratment of hypotension with dopamine and arrhythmia with an antiarrhymic drug (Quindine-procainamide)

Lead

Exposure: the major routes of lead intry into the body are GIT(igestion) , lungs (inhalation) and demal absorption (insignificant except in the case of organic lead) .

Childern may ongest leaded paints or other articles containing lead such as newspapers, toys, pencils and plasters.

Inhalation of lead is hazad in battery industry, stained glasd window production. Toxicity may occut in addicts using methamphetamine by intravenous injection since lead acetate contaminant is used during the manufacture of phenyl-2- propane, a precursor of methamphetamine. Organic lead compoun (**tetraethyl lead**) may be absorbed through intact skin. Lead is distributed through out soft tissues; bone is the principal storage area.

Mechanism of toxicity:

Lead react woth sulfhydryl group of proteins, thus it interferes with enzymes containing sulfhydryl group. It interes with enzymes of heme synthesis for hemoglobin production.

Symptoms of acute poisoning:

1-GIT: burning sensation in mouth, esophagus and stomach followed bt severe abdominal pain. Loss of appetite, metallic taste, colic, vomiting and constipation.

2-CNS: restlessness, irritability, convulsions, and coma.

3-Blood:anemia and hemolysis

4-Kidney and liver functions are impaired with the presence of blood in urine.

Symptoms of chronic toxicity (plumbism)

1-GIT: anorexia, loss of weight, metallic taste, abdominal pain and constipation. Chronic toxicity of lead is characterized by the presence of black line on the gum the border of the teeth.

2-Red cells: anemia, which is due to interference with the synthesis of hemoglobin.

3-Lead encephalopathy: in adults, symptoms may be limited to irritability. In children a condition known as lead encephalitis may develop. This condition is characterized by irritability, insomnia, headache, and restlessness, losd of memory, convulsions and coma.

4-Leaf palsy or myopathy. This condition is characterized by peripheral neuritis, paralysis, wrist and foot drop.

5-Cardiovascular: hypertension may occur with chronic exposure.

6-Kidney: fanconi-like syndrome (proteinuria, hematuria, amino-aciduria and phoshpaturia) may occur, ultimately leading to chronic interatitial nephritis and renal failure.

7- reproductive: lead poisoning may produce decreased sperm count or an increased number of abnormal spetm. In women it produces steriity , miscarriages and when birth occurs normally the infant mortality rate during the first year is high.

Diagnostically, blood lead levels in the range of 30-60 ug/dl along with these symptoms may indicate chronic lead poisoning.

Treatment:

1-**GIT decontamination:** It is not recommended unless lead is visible, on abdominal - radiographs. If lead seen on the radiograph, whole bowel is irrigation should be .considered

2-Antidotes

a-BAL chelates lead both intra- and extra-cellularly. Two molecules of BAL combine with one atom of lead to form a complex that is ***excreted*** in the bile and urine.

b- Calcium disodium ethylenediamine tetraacetic acid (CaNaz EDTA) removes lead from the extracellular compartment and increases the urinary. Excretion **20-50 .fold.**

c-Coposu DMSA is an orally active water-soluble chelator. It may remove lead from the bone and soft tissues. It does not deplete essential metals as do **BAL and CaNaz EDTA.**

MERCURY

Sources of poisoning: Three main types of measury may cause toxicity. These types are the **elemental mercury, inorganic mercury and organic mercury**

1 Elemental mercury

It is the only elemental metal that is a liquid at room temperature. It is **used** in glass thermometers, sphygmomanometers, amals, nuorescent lamps and paines **Inhalation** is the main route of absorption Spilled mercury vapores readily and can be inhaled, where it is rapidly absorbed in the lungs. Once in the bloodstream, it distributes to all tissues and crosses the placenta and blood brain barrier, is is excidized to divalent mercury after absorption Elemental mercury is poorly absorbed in the gastrointestinal tract and toxicity is rare.

2 Inorganic mercury

It is present in divalent form (Hg. mercurie) or monovalent (Hg, mercarous) Mercuric salts (e.g., mercurie chloride and mercufic nitrate) have been used as antiseptic and in other industrial processes. Mercurous chloride (calomel) is used as a teething powder and laxative, **Ingestion and dermal** contamination are the main routes of absorption of inorganic mercury.

3 Organic mercury

It occurs in different forms, Methyl and ethyl mercury are environmental contaminants of aquatic food chain involving plankton and herbivorous fish.) **Ingestion** in the main route of absorption of organic mercury.

Mechanism:

Mercury produces inhibition of **sulfhydryl enzyme** systems and interfering with cellular metabolism and function. Mercury also reacts with phosphoryl, carboxyl and amide groups, resulting in widespread dysfunction of enzymes, transport mechanisms, membranes and structural proteins.

Signs and symptoms:

A-Inhalation:

Elemental many on cause bronchitis, fever, chills dyspnea, pulmonary edema and lung fibrosis, CNS damage is manifested as tremors, depression and insomnia.

B- ingestion:

1-GT: gingivitis, stomatitis, esophageal erosions, nausea, vomiting hematemesis and
2- Circulation: Rapid irregular pulse low blood severe abdominal camping pressure, collapse and myocardial damage.

Chronic poisoning:

Chronic exposure (ingestion or inhalation of contaminated water or foods) yields a classic triad of gingivitis and salivation, tremor, and neuropsychiatric changes. **Acrodynie (Park disease)** is associated with the use of **calomel (mercurous chloride)** in children and mentists as color changes in the tips fingers, toes and ankles.

Laboratory tests: Screening tests, including 24 hour urine collection, electrolytes, blood urea nitrogen (SUN), creatinine, and urinalysis, are all indicated. A normal blood mercury level is <10 gm/L

Treatment:

1-Decontamination: Removal of patient from further exposure. Emesis should be induced except after organic salts intoxication and if patient is alert and , Gastric lavage and activated charcoal are not recommended in elementary mercury poisoning. However, they may be used after organic salt ingestion within 1 hour. Whole bowel irrigation may be useful.

2- **Antidotes:** Oral **DMSA** (**soccimer**), a chelating agent enhances renal excretion of mercury . Immediate intramuscular administration of BAL may prevent renal toxicity of inorganic salts. Penicillamine for symptomatic acute mercury exposure.

3-Supportive measures: treatment of pulmonary oedema. Controlling of seizures with intravenous diazepam.

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 usually produce poisonings. Ingestions of less than **20 mg/kg** of elemental iron 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 hemósiderin. Normally excess ingested iron is excreted and some is contained within shed intestinel cell, in late and see amounts in sweat, nails and hair.

Clinical manifestations

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

Stage 1 (0.5-6 hours)

Symptoms usually occur within **6 hours** of ingen schy nausea, vomiting, dianhea and abdominal pain. Direct corrosive effec in gastrointestinal mucosal injury Shock dus to blood or fluid loss, lead to hypoperfusion, which may contribute to the development of metabolic acidosis. Release of hydrogen long when iron is oxidized from the ferrous to 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 tests 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 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 to the jejunum, Aggressive intervention, with antidotal therapy and the stomach to the .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 tests:

1-Deferoxamine test: it is performed by mixing 2ml 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 ug/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. H_2 po 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.

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.

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

PESTICIDES

Pesticides are Chemical agents intended for killing any pest. The term pest includes unwanted species of animals, plants or microorganisms.

A. Insecticides

These are chemical agents used to kill insects or to make them unable to function as a pest. The most important insecticides may be subdivided into the following groups

1. 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 acetylcholinesteras (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 .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, Lacrimation, Salivation. In addition to Bronchospasm and bronchorre, Emesis bradycardia, cardiac conduction, disturbances can result from 'augmental vagal ton.

2-Stimulation of nicotinic receptors at the neuromuscular junction causes muscle result weakness, fasciculation and paralysis. Effects at ganglionic nicotinic receptors in diaphoresis, mydriasis, tachycardia and hypertension, which most appear in the course of poisoning.

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

Laboratory diagnosis

Gas chromatographic techniques can detect organophosphate metabolizes of malathion, parathion and diszinon in both blood and urine. Blood samples should be drawn to measure plasma pseudocholinesterase and red blood cell AChE levels. Depressions of plasma pseudocholineste and/or acetylcholinesterase 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 with artificial respiration for several days. Tissue oxygenation is essential prior to atropine administration, 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 d 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 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 & Convulsions can be controlled with intravenous diazepam, Phenobarbital or phenytoin.

D-Antidotes

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 minute until signs of atropinization appear *(flushed face, dry mouth, dilated pupils and fast pulse)*

Glycopyrolate.

It can be used 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

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 500st as mg/bours is sufficient to serum-levels in most cases.

2-Carbamate insecticides

Carbamate insecticides are widely used in homes, gardens, and agriculture. They can be absorbed orally, by inhalation and somewhat by skin penetration, although the latter tends to be the less toxic route. Examples include methomyl, carbaryl, carbofuran and aldicarb.

Mechanism of toxicity

The carbamate insecticides cause reversible carbamylation of the acetylcholinesterase enzyme, producing accumulation of acetylcholine and the picture of muscarinic and nicotinic poisoning Carbamates differ toxicologically from organophosphates by the relative affinity of their binding to cholinesterase and their duration of effect; carbamates spontaneously hydrolyse from the cholinesterase enzymatic site within 24 hours, whereas organophosphates do not.

Clinicl manifestation

Carbamate insecticides produce a mild form of toxicity, similar to that produced by poorly penetrate :organophosphate compounds. Unlike organophosphates, carbamates the blood brain barrier, resulting in limited CNS effects. Convulsions and bradycardia are less common than in organophosphate poisonings.

Management of toxicity

Patients poisoned with carbamate insecticides should be managed identically to those intoxicated with organophosphates. Atropine is the antidote of choice in carbamate poisoning. PAM is indicated if a patient with known carbamate poisoning does not respond to atropinization.

3- Pyrethroid insecticidest.

The Insecticide pyrethrum is derived from the ground, dried flower of Chrysanthemum cineriifolium, pyrethrum is made up of six active chemicals called pyrethrins. Pyrethroids are synthetic derivatives of these compounds developed because of the relatively high cost, high biodegradability and light instability of natural

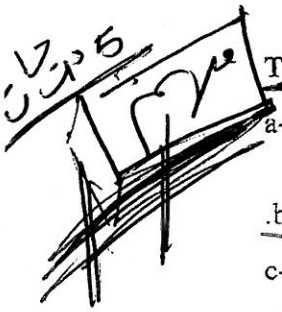
pyrethrum.Alletrin, permethrin, deltamethrin and cypermethrin are examples of synthetic pyrethroids.

Mechanism of toxicity

Pyrethroid insecticides affect the activation (opening) and inactivation (closing) of the sodium channel, resulting in a hyperexcitable state. They di calcium channels and Ca, Mg, ATPase.

Signs and symptoms of poisonings

Hypersensitivity reactions, contact dermatitis, cough; rhinitis and asthma are the most commonly reported symptoms. Ingestion caused epigastric pain, nausea, vomiting, headache, dizziness, anorexia, fatigue, blurred vision, parethesia, palpitations and muscular fasciculations, Parethesis resulting from these agents are thought to be secondary to chemical activity on cutaneous sensory nerve endings. In severe poisonings, convulsivo attacks and loss of consciousness have comes.



Treatment of Pyrethroid ?

a- Symptomatic and supportive measures may be required for bronchongaum an .anaphylaxis.

.b- Decontamination of the eyes and the skin is suggested .

c- Oral or topical antihistamine and corticosteroids administration can be used of dermatitis.

d- Vitamin E oll is applied topically to relieve cutaneous parethesia following Skin contact.

e -Benzodiazepines and barbiturates are effective in controlling pyrethro induced tremors and seizures.

Botanical insecticides

A number of naturally occurring agents of plant origin have been used to control insects

Nicotine

Exposure to nicotine occurs during processing or extraction of tobacco, during application of insecticides containing nicotine or during smoking. Nicotine is readily absorbed through the skin and mimics or blocks, depending on the dose, the action of acetylcholine at all ganglionic synapses and at neuromuscular junction. As an insecticide, nicotine blocks synapses associated with motor nerves.

Rotenoids

Rotenoid esters can be isolated from the plants Derris elliptical. Rotenone, one of the alkaloids, can be used topically for treatment of head lice and scabies. Rotenone blocks electron transport in mitochondria by inhibiting oxidation linked to NADH2, Cave conduction blockade. Rotenone dust is highly irritating to the eyes resulting (causing upper respiratory tract (causing ,(ct dermatitis causing contact) conjunctivitis), skin thinitis) and throat (linked with pharyngitis). Acute poisoning is characterized by initial respiratory stimulation followed by respiratory depression ataxia, convolutions and ,death from respiratory arrest.

B. Herbicides

Herbicides are chemical compounds used to eliminate unwanted plants .

1-Chlorophenoxy herbicides

The most common agent are 2,4-dichlorophenoxyacetic acid and 2,4.5.trichlorophenoxyacetic acid. These compounds are weak acids that are excreted highly unchanged in the urine The compounds are Protein bound.

Routes of exposure

The most common exposure is intentional ingestion. Chlorophenoxy compounds are well absorbed from the gastrointestinal tract. They are less well absorbed from the lung. Absorption of these herbicides across intact skin is relatively.

Clinical toxicity

Chlorophenoxy compounds, are moderately irritating to skin and mucous membranes. Inhalation of sprays may cause burning sensations in the nasopharynx anorexia, burning sensation in the mouth, gastrointestinal ulceration, nausea vomiting, diarrhea and fatigue. **High level exposure** may uncouple oxidative phosphorylation, leading to agitation.CNS effects following pyrexia, tachycardia, hyperventilation and severe massive ingestion include muscle fasciculation, ataxia and coma

Laboratory findings

Myoglobin haemoglibin may be found in the urine. Elevation in lactate dehydrogenase, creatine phosphokinase, aspartate aminotransferase and alanine aminotransferase indicate the extent of muscle damage. The ECG should be monitored for the possibility of cardiac thytham abnormality.

Management of toxicity

1-If any symptoms of illness occur following inhalation of spray, transfer the victim to fresh air.

2-Wash contaminating chemicals from eyes with large amounts of water. If irritation persists, an ophthalmologic examination should be achieved

3-Gastric decontamination procedures may be considered if substantial amounts of chlorophenoxy compounds have been ingested

4-Administer intravenous fluid to accelerate excretion of the chlorophenoxy compounds, and to limit concentration of the toxicant in the kidney

5-Forced alkaline diuresis by including sodium bicarbonate in the intravenous solution accelerates excretion of these weakly acidic compounds

6-Hemodialysis is not likely to be of significant benefi

7-Give lidocaine for cardiac rhythm abnormality

2-Bipyridyl herbicides

Paraquat is the best-known compound of this class of herbicides. It includes diquat

Chlormequat ,mepiquat and difenzoquat. Although some exposure may occur through contact with skin or mucous membranes, almost all fatalities have occurred following intentional ingestion. Chronic occupational exposure to paraquat does not appear to cause pulmonary toxicity More than 90% of the absorbed dose of paraquat is eliminated by the kidneys within the first 12-24 hours after the ingestion.

Mechanism of toxicity

paraquet NADPH Paraquat concentrates in lung due to the presence of polyamine system in the alveolar cells. In the pneumocyte, paraquat can be reduced transporter by NADPH- dependent microsomal flavoprotein reductase to form the monocation radical. This then reacts with molecular oxygen to yield the superoxide radical and reform the paraquat dication, which can be reduced again. Superoxide radicals destroy membranes, damage alveolar integrity and induce fibrotic changes lipid.

Clinical manifestations

Ingestion of paraquat causes burning in the mouth, vomiting, oliguria, Soesophageal ulceration and upper GIT bleeding and ulceration. Severely poisoned patients show fever, tachycardia, respiratory distress, cyanosis, convulsion and coma. Inhalation of paraquat either as spray or by smoking contaminated marijuana could cause delayed pulmonary edema without immediate symptoms. Patients have died of weeks after poisoning.

Tratment

1-Administration of absorptive agents such as activated charcoal or Fuller's Earth may be useful, because paraquat may be deactivated after coming in contact with such absorptive materials.

2-In the first 2 hours following ingestion, upper GI endoscopy is recommended to identify the extent and severity of any mucosal lesions in the esophagus or stomach.

3-Maintain urine output at [illegible] by gi[illegible] intravenous and furosemide if necessary.

4-Elimination enhancement using haemodialysis or haemoperfusion is effective within 10-12 hours, before absorbed paraquat is distributed extensively to tissues but less effective thereafter.

5-Hydrocortisone and large doses of vitamins C and E (as antioxidant) may be helpful early.

Note

Diquat has similar properties to paraquat but does not selectively concentrate in lung tissue, so respiratory failure is much less likely.

C. Rodenticides

Rodenticides are chemical agents used to kill rodents such as rats, mice and squirtels All rodenticides are non elective, highly toxic and are generally hazardous.

Classification

1-Highly toxic rodenticides (LD50 <50 mg/kg) -

a- Thallium sulfate

Thallium sulfate lethal to most animals in doses of 10-20 mg/kg.

Mechanism: It combines with mitochondria-SH groups, interfering with oxidative phosphorylation.

Symptoms: GIT symptoms appear 1-2 days following ingestion and include nausea, vomiting, bloody diarrhea and abdominal pain. Neurologic symptoms occur 2-5 days

after exposure and include headache, muscle weakness, tremors, convulsions, leg pain, parathesia of the hands and feet and coma.

Treatment: includes gastric lavage and administration of activated charcoal.

b-Sodium fluoroacetate

Mechanism: Fluoroacetate inhibits the enzyme aconitase and thereby prevents the conversion of citrate to isocitrate in the krebs cycle. Inhibition of the Krebs cycle decreases glucose metabolism, cellular respiration and tissue energy stores.

The symptoms include cardiac irregularities, renal failure, convulsions and death from ventricular fibrillation or respiratory failure.

Treatment: Lavage followed by a sorbitol cathartic is recommended. There are no known antidotes to fluoroacetate intoxication.

C-Zinc phosphide:

Mechainsm: Zinc phosphide reacts with water and hydrochloric acid in GIT to produce phosphine gas which causes necrosis of the gut and injury to other organs such as liver and kidneys.

Signs of intoxication include vomiting, diarrhea, cyanosis, tachycardia, fever, restlessness, hypertension, pulmonary oedema and convulsions.

Treatment includes dilution with sodium bicarbonate, milk or water followed by gastric lavage, activated charcoal and a cathartic.

d-Strychnine

Strychnine is a tasteless, odorless crystal that is absorbed through the GIT or nasal mucosa. It is a highly toxic rodenticide used for this purpose since 16 century.

Mechanism: Strychnine competes with the inhibitory neurotransmitter glycine within the brain stem, spinal cord and higher centers. **Symptoms:** It is a CNS stimulant twitching, extensor spasm, opisthotonos, seizures and medullary that causes muscle paralysis resulting in death.

Treatment: Early useful interventions include the use of activated charcoal and orogastric lavage. The extensor spasm and convulsion may be controlled initially with diazepam followed by Phenobarbital or a neuromuscular blocking agent. Intubation and

mechanical ventilation are also required .

2-Moderately toxic rodenticides (LD50: 50-500 mg/kg): -

a-Alpha-naphthyl thiourea (ANTU)

ANTU kills rats by causing pulmonary oedema and pleural effusion probably of damage to the lung capillaries resulting in increased permeability. Green Jeep **Symptoms of** toxicity include dyspnea secondary to pleural effusion, because cyanosis and hypothermia.

Treatment for ANTU ingestion is orogastric lavage followed by administration of activated charcoal and a cathartic.

B- Cholecalciferol

In rodents, mechanism:cholecalciferol (vitamin D3) mobilizes calcium from bones and

In toxic doses produces hypercalcemia, osteomalacia and metastatic calcification of the cardiovascular system, kidney, stomach and lung; death typically occurs in 2 to 5 days.

Tratment: Immediate intervention after a large acute ingestion should include gastric emptying by emesis or orogastric lavage followed by gastric decontamination with activated charcoal and sorbitol.

Treatment for moderate to severe degrees of hypercalcemia include intravenous fluid therapy with 0.9% sodium chloride solution if the patient is hypovolemic and can tolerate a fluid load. Calcitonin may reduce serum calcium levels over a few hours by inhibiting osteoclastic bone restoration while promoting calciuria

3-Low toxicity rodenticides (LDs: 500-5000 mg/kg)

Anticoagulants

The most common anticoagulant rodenticides are warfarin and superwarfarins. Superwarfarins (e.g., brodifacoum, difenacoum) are so named because they are designed to be effective against even warfarin-resistant rodents. Although their mechanism of action is identical to wafarin, superwarfarins can be lethal to rodents after just one dose as opposed to the estimated 21 days of feeding needed with warfarin, This occurs because superwarfarins have much higher lipid solubility and are more selectively concentrated in hepatic cells. In addition, the plasma half-life of superwarfarins is about 156 hours, compared with wafarin's half-life of about (37) hours. Brodifacoum is, therefore, a more efficient rodenticide because it is to exert its effect in smaller amounts and eliminate the need for frequent feedings.

Mechanism of toxicity

Warfarin and superwarfarins alter the synthesis of coagulation factors in the liver by interfering with vitamin K-mediated gamma carboxylation of precursor coagulation factor proteins. The factors affected are II VII, IX, and X. The antiprothrombin effect is best known, and is the basis for detection and assessment of clinical poisoning. The

agents also increase permeability of capillaries throughout the body, predisposing the animal to widespread internal hemorrhage.

Clinical presentations

Clinical effects of these agents include oral bleeding, upper GI bleeding. hematuria and paralysis due to cerebral haemorrhage. Patients may also have symptoms of anemia, including fatigue and dyspnea on exertion. If the poisoning is severe, the patient may progress to shock and death.

Management of toxicity

Gastrointestinal decontamination: Activated charcoal may be helpful shortly after ingestions. Gastric lavage may induce GI bleeding. Ipecac may cause intracranial haemorrhage by increasing intracranial blood pressure.

Determine prothrombin time: Measurement of prothrombin time should be performed 24-36 hours after exposure to identify patients at risk of coagulopathy.

Elimination enhancement: Forced diuresis, haemodialysis and charcoal haemoperfusion are not useful..

Antidote: The goal of therapy for anticoagulant rodenticide ingestion is to reverse the coagulopathy and replace blood loss. Fresh frozen plasma is the treatment of choice when there is active bleeding Vitamin K administration is required if long-term anticoagulation is anticipated. Vitamin K_1 (phytonadione) is more active and also works more rapidly than other vitamin k preparations (K3, menadione and K_1, menadiol). It can be given orally. subcutaneously or intravenously. Intravenous administration of vitamin K is slightly faster than oral dosing at correcting a prolonged prothrombin time. However, the intravenous route is also associated with an increased risk of cardiorespiratory depression, possibiy because of anaphylaxis or an anaphylactoid reaction.

CHEMOTHERAPY

Is the use of synthetic chemical substances against infective organisms.

Antibiotics: Is a substance produced by a living micro - organism which in high dilution inhibit or kills another microorganism.

N.B. Broad spectrum antibiotics usually have ↓ efficacy While narrow spectrum are usually cidal.

* Narrow spectrum e.g., Penicillin, Cephalosporisn Erythromycine Aminoglycosides and Sulphonamides.

* Broad spectrum e.g. Tetracycline, Chloramphenicol, Quinolones..

* Bactericidal (to kill bacteria): Penicillins, Quinolones , Cephalosporins.

* Bacteriostatic: (↓ growth) chloramphenicol tetracycline, sulphonamide.

CLASSIFICATION OF ANTIMICROBIAL

I. Inhibitors of cell wall synthesis

1st step . synthesis of peptidoglytcan (di-alanine) in cytoplasm ≠cycloserine.

2nd step : Peptidoglycan transfer (elongation) to cell wall ≠(vancomycin, Bacitracin.

3rd step : Cross linkage formation by transpeptidase ≠ B-Lactams)

A. B-Lactam antibiotics

1- Penicillin's.

Mechanism :combine with PBP→↓ Transpeptidase →↓ cell wall synthesis in growing bacteria →↓ rigidity and resistance to change in O.S. → "Bacteriocidal". Also ↑ autolytic enzymes.

Spectrum : +ve and -ve cocci, +ve bacilli, spirqchaetes($,lyme disease, relapsing fever)actinomyces. More active against thick cell wall (Gram +ve) than thin (Gram -ve) which has an outer lipopolysaccharide membrane, so only pass through water channels(porins) .No porins in pseudomonas.

Broad spectrum penicillin's → affect also - ve bacilli.

Resistance: 1- Common with strains that produce β lactamase eg S. aureus, Disrupts B- lactam ring → loss of activity.

lteration of penicillin binding protein (PBP).

ire of drug to cross outer lipid mem. to reach transpeptidase (gm –ve)

:e of efflux pump.

N.B2. unlike ampicillin, amoxycillin →↑ absorption, B1. Levels, duration, tissue penetration, ↓ diarrhea more potent on sallmonella than shigella.

NB3: Except amoxycillin food ↓ absorption of oral penicillins→ keep 2h. from food.

Distribution : Extracellular + intracellular, cannot pass BBB. But in meningitis → inflammation → V.D. → Penicillins pass BBB

Excretion : 90% active tubular, 10% glomerular filtrate.

Probencid → Block active excretion → long duration.

Uses :

A. Treatment:-

1- Strept, staph., pneumococcal enterococal infections (+ve cocci).
2- Gonrrhoea, meningococcal infection (-ve cocci).
3- Anthrax, Diphtheria, tetanus (+ve Bacilli).
4- Broad in Typhoid and paratyphoid but ciprofloxacin 1st choice.
5- Actinomycosis, gas gangrene, $,lyme disease, rat bites fever.

NB: PenicillinG is DOC in diphtheria(corynebactrium),tetanus, gas gangrene (clostridia)

B. Prophylactic:

* Rhumatic fever → Benzathine penicillin.
* To prevent subacute becterial endocarditis → procaine penicillin (cephlsporin better). *Agranulocytosis.
* To prevent gonorrheal ophthalmia in neonates ; Benzyl penicillin eye instillation.

Adverse effects:

1- Allergy (5-20%) : may occur even é 1st injection.

a- Skin rash : up to 9% é ampicillin. b- Angioedema. c- Eosinophilia

d- Herxheimer reaction with $: Fever for 2days don't stop + cortisol

e- Anaphylactic shock (1/50000) : Ttt: Adrenaline (life saving), +corticosteroid, + antihistaminic. Never use penicillin.

f- Cross resistance : é other types & é cephalosporins. Replace é vancomycin, erthromycin, co-trimoxazole.

2- CNS irritation with very high doses. 3- Diarrhea (superinfection)

4- Interstitial nepheritis é methicillin. 5- Hepatic and renal dysfunction (rare).

2- Cephalosporins

Mechanism, distribution, Excretion → Like penicillin.

Spectrum : Broader than penicillin but not in : Typhoid, $, enterococci.

Less allergic reactions, more penicillinase resistant.

Generation	Route	Elimination	Gram +ve	Gram - ve
1st: least toxic			+++	+
Cephalexin, cephardin, (cefadroxil : long acting)	Oral / im	Renal		
Cephazolin, cephalothin, cephalordine.	Iv / im	Renal		
2nd			++	++
Cefaclor	Oral/iv/im	Renal		
Cefamandole, cefoxitin,moxalactam	iv/im	Renal		
3rd			+	+++
Cefixime, cefpodoxime	Oral	Renal		
Cefotaxime, ceftazidime	Iv/im	Renal		
Ceftriaxone, cefoperazone	Iv/im	hepatic		

N.B: 3rd generation and cefepime or cefpirome (4th generation iv): ↑ (pass BBB, B-lactamase resistant, spectrum, efficacy, against pseudomonas and anaerobes)

Uses:

1- 1st choice in Klebsilla pneumonia. (Cephazolin)

2- 2nd generation useful in H. influenza.

3- 3rd generation (cefotaxime, ceftrixone in meningecoccal meningitis, UTI)

4- Gonorhea (ceftriaxone) 1st choice 5- Septicemia (iv).

6- Respiratory & Urinary Gram-ve infections. 7- surgical prophylaxis:cephazolin.

8- Staph. Infections e.g. osteomyelitis & pneumococal pneumonia,

Side effects:

1- Allergy (10% cross allergy é penicillins), local : thrombophlebitis

2- Superinfection. 3- Disulfiram like:cefoprazone,moxalactam.

4- ↑ nephrotoxicity of frusamide & aminoglycosides. ↑ with cephardin.

5- Bleeding tendency: hypoprothrombinemia with cefamandole and ↓ platelet aggregation with cefoprazone, moxalactam, (3rd): give vit K.

3- Monobactams . e.g Aztreonum (iv, im)

B-lactamase resistant, narrow spectrum affect Gram-ve only e.g. pseudomonas.

*No cross allergy with other B-lactamas. **Use:** Gram-ve meningitis

Side effects : Superinfection. e.g. Pseuomembranous colitis.

4- Carbapenems e.g. imipenem (iv)

- Broadest spectrum against aerobes and anaerobes, even non growing.
- B-lactamase resistant. Inactivated in renal tubules by dihydropeptidase. → given with cilastatin forming tienam which inhibit the enzyme → prevent nephrotoxicity.

Side effects : Seizure, Nausea, vomiting , allergy & cross allergy é penicillins

Etrapenem,meropenem: not degraded in kidney nor Seizure

B-Vancomycin (iv), tecioplanim

* Poor absorption, Pass BBB in meningitis excreted by kidney
* B- lactamase resistant, affect G. +ve.

Uses : 1- Methicillin resistant staph. Drug of choice

2- Staph enterocolitis & pseudomembranous colitis (oral).

Adverse effects : 1- ototoxicity 2- Nephrotoxicity specially with aminoglycosides. 3- Red man syndrome (Histamine release).

C- Bacitracin (local only)

* Affect G + ve, B-lactamase resistant.
* ↑ Nephrotoxic * Given é polymexin & neomycin topically.

D- Cycloserine

* **Used** in T.B. resistant to 1st line drugs.
* **Adverse effect** : headache, confusion, tremors, seizures.

II- Cell membrane inhibitors

1- Polymyxin : bactericidal, G-ve, Nephrotoxic, Not absorbed → oral on GIT.

2- Antifungal : Nystatin, amphatercin B, Azoles, terbinafine naftifine, tolnaftate (See antifungal).

III- Protein synthesis inhibitors

1 - Aminoglycosides

Mechanism: Binds to cell membrane→ active uptake into cytoplasm(o_2 dependent) → attach to ribosome's (30S) irreversibly →↓ attachment of m RNA to ribosome's & misreading of genetic code →↓ synthesis of normal proteins & ↑ synthesis of lethal proteins → bactericidal.

Spectrum : Mainly gram -ve bacilli(not typhoid) + some (+ve) cocci. Not against anaerobes where there is no active uptake.

Resistance & cross resistance in between it are rapid due to :

* ↓ Permeability of cell wall.

* Altered the receptor ribosome.

* Development of enzymes that destroy the drug (most common).

Absorption : Poor from G.I.T. → If oral → local on GIT(not destroyed by HCL) e.g. to sterilize bowel before surgery, Intestinal infections (Bacillary dysentery), hepatic coma.

Distribution : Extracellular, pass BBB only in meningitis, Pass PB

Excretion : 1- Renal in free form. Renal failure → accumulation → toxicity (contr.). 2- Milk, Bile, tears.

Adverse effects (↓ safety margin):single daily dose safe , more effective.

1- **Ototoxicity** : 8th cranial nerve damage (Irreversible) more with loop diuretics aspirin. vertigo (streptomycin), Deafness. (amikacin).

2- **Nephrotoxicity:** more é gentamycin & potentiated by cephalosporins. Reversible

3- N.M. Block (intrapleural) → respiratory paralysis. **4- Allergy**

5-Oral:superinfection,diarrhea, ↓V.K production and cholesterol level.

* Badcriostatic e.g Chloramphenicol: ↓ cidal e.g aminoglycosides.

Bactericidal:↓ cell wall →↑entrance of amninoglycosides (cidal) = synergism,..But never given in the same container because aminoglycoside are strong base and penicillin acidic then, they will be inactive.

Members and uses:

Streptomycin (im): the only with ↑ PPb. Uses :

1-T.B. (not alone). 2- Urinary T. infection (Alkaline urine →↑ activity).

3- Bacterial endocarditis with penicillin G.(↓resistance, ↑spectrum).

4- Brucellosis and plague: used é tetracyclines. 5- Local.

Gentamycin : im, iv, topical,intrathecal in meningitis but cefotaxime better.

Use: like streptomycin but in acute, sever resistant cases (↑ toxicity)

Tobramycin : Like gentamycin but more against pseudomonas: no porins.

Amikacin & netilmicine : Not affected by inactivating enzymes → less resistance.

Kanamycin and **Neomycin** : Broader spectrum but very toxic → local only:

a- G.I.T. (oral). B- Skin & mucous mem. (Topical).

c- Hyperlipidemia (oral): ↓ Bile acid absorption→ ↓ cholesterol.

2- Macrolides

Erhythromycin

Mechanism : Interferes with protein synthesis in bacteria (site 50s). conc.

Or organism→ bacteriostatic or bactericidal.

Spectrum: Like penicillinG. **Distribution** : all over the body excerpt brain.

Resistance: 1- Reduced permeability of cell membrane

2- Production of Esterase that hydrolyse macrolides.

3- modification of ribosomal binding site.

Absorption : The estolate esters only is acid resistant →Oral.

Excretion : biliary and renal (5%).Not in liver disease.

Uses:

1- Allergy or resistance to penicillin.

2- Atypical pneumonia caused by Mycoplasma, Legionella (No cell wall→Cell wall inhibitors not effective). 3- Diphtheria. 4- Bordetella pertusis.

5-UTI infections by chlamydia in pregnancy or infancy.

6- Gonorrhea, syphilis. 7- Gastroenteritis caused by Campylobacler jejuni.

Side effects: One of the least toxic antibiotics.

1- GIT irritation: nausea, vomiting diarrhea.

2- Acute cholestatic hepatitis: due to Estolate Ester.not in liver disease.

3- Erythromycin or telithromycin: enzyme inhibitor →↑ action of many drugs e.g.Warfarin,Carbamazepine, Theophylline. with Astemizole or Terfenadine →Arrhythmia .Kill flora that inactivate digoxin→↑BL.conc.

* **Clarithromycin, azithromycin**like erhythromycin but wider spectrum absorbed from GIT,longer,expensive,lessGITdisturbance, No enzyme inhibition e.g. affect sallmonella,↓ H.pylori- reversible deafness. Clarithronycin more active against toxoplasma, Mycobacterium avium,lepra.Azithromycin less active on staph,strep more onH.influenza **Telithromycin:** Like erythromycin but acid stable, less resistance, prolong QT, Produce arrhythmia and visual disturbance.

3- Clindamycin

Mechanism : like erythromycin but always bacteriosttic.

Spectrum : Gram + ve, anaerobes except enterococci. **Absorption** :Good.

Distribution : Good but not pass BBB even in meningitis.90%PLPB.

Metabolism : liver. **Excretion** : urine, bile.

Use : 1- 1st choice in anaerobic abdominal infections (Bacteroids e.g. B fragilis).

2- penetrating wounds 3- prophylaxis of endocarditis.

4-With pyrimethamine in toxoplasmosis.

Resistance : enzymatic inactivation, ribosomal mutation.

Adverse effect : Pseudomembranous colitis Ttt vancomycin,metronidazole

N.B.Chemotherapeutics in anaerobic infection:

1-Clindamycin.2- Metronidazole. 3- generation 2,3,4 cephalosporin.

4- Imipenem. 5- chloramphenicol. 6- penicillin (+ve)

✳ 4- Chloramphenicol ✳

Mechanism : Inhibit reversibly protein synthesis (50s). Bacteriostatic.

Spectrum : Broad. Including rickettsia. Not Chlamydia.

Resistance : Slow and temporal due to : 1- inactivation by acetyl transferase produced by organism. 2- ↓bacterial cell wall permeability.

Absorption : ↑↑↑ from G.I.T. but ↑ toxicity limit its use.

Distribution : extracellular + Intracellular + C.S.F. Not in pregnancy or lactation.

Metabolism : Liver. **Excretion** : Renal.

Uses : 1- Rickettsial diseases. 2- Anaerobic infections. 3- eye infections.

4- Typhoid & paratyphoid. 5- Meningitis, gonorrhea, pneumonia, $, UTI

✳ ***Side Effects:*** limits it use

1- Bone marrow Inhibition:↓ (RBCs, leukocytes, thrombocytes).

* Reversible dose dependent: RBC_s mainly.

* Irreversible fatal aplastic anemia (idiosyncrasy): 1/4000 – Not dose related.

2-Graybabysyndrome:shock, gray skin:deficient conjugation and excretion

3- Superinfection, GIT Upsets. 4- Optic and peripheral neuritis.

Drug interaction : 1- ↓ liver microsomal enzymes →↑ activity of drugs e.g.

Warfarin , Tolbutamide,chloroprpamide,pheytoin,theophylline.

2- ↓ bactericidal effect of penicillin & aminoglycosides.

5- Tetracycline's

Mechanism : Attach weakly & reversibly (unlike aminoglycosides) to bacterial ribosome (30s) → prevent attachment of tRNA to m RNA → prevent addition of amino acid to peptide chain →↓ protein synthesis →bacteriostatic.

Spectrum : Broad including protozoa, chlamydia, treponema, rickets but not typhoid.

Resistance : Uncommon but cross resistance occurs due to:

* Alteration of outer membrane proteins. * Enzyme inactivation.

* Active transport out by microorganism (plasmid mediated).

	Tetracycline, oxytetracycline, demeclocycline, chlortetracyline	**Doxycycline, minocycline.**
Absorption	**Not complete from G.I.T.:** Sterilize intestine. Suprainfection. Ca^{++}, Al^{+++}, Milk, ↑ PH, →↓ absorption.	Complete,rapid (lipid soluble) Enterohepatic cycle→ Long duration (24 hs).Not reduced by food.
Distribution	Extracellular	Extra + intracellular.
Excretion	Renal → cummulation in renal failure.	No cummulation (eliminated by liver).

Uses:

1- 1st choice in: Mycoplasma (atypical pneumonia) Rickettsiae (typhus, Rocky mountain spotted fever) Chlamydia (lymphgranuloma venerium, peneumonia).

2- Brucellosis. 3- Acne. 4- Lyme disease, relapsing fever.

5- GIT. infection: intestinal amebiasis, bacillary infection and cholera.

6- Syndrome of inappropriate ADH secretion↑ (SIADH): Democlocycline.

7- Topically in skin and eye infection. 8- UTI.

8-**Tigecycline** (36 h.) in acute amyloid leukemia.

Adverse effects : Limits its use.

1- G.I.T. disturbance : Nausea, vomiting & diarrhoea. 2- Allergy

3- Superinfection : candidiasis, pseudomambranous colitis.

4- Photosensitivity , Nephrotoxicity and D.I. é demeclocycline.

5- enamel hypoplesia : Chelate Ca++ from teeth and bones → yellow teeth. Pass placental B. → affect fetus contr. Pregnancy. Excreted in milk → affect baby contr lactation or children under 12 years.

6- Hepatotoxicity & cholestatic jaundice specially é pregnancy.

7- Fanconi syndrome : with expired preparations. 8- Teratogenic.

9- Vestibular toxicity é minocycline. 10- potentiate oral anticoagulants

11- Enzyme inducers →↓ duration & action of doxycycline & minocycline.

6- Na fusidate.

* Effect G+ve(50S) mainly B. lactamase producing staph. * Use : Osteomyelitis.

7-Oxazolidinones eg.Linezolid(Averozolid)NEW

* Effect G+ve(50S) resistant to others .MRSA resistant to vancomycin.

*Static but cidal against some strains of pneumococci, Bacteroides fragilis and C. perfringens.

IV - Inhibitors of nucleic acid synthesis

1- Folate antagonists: a) Compete with PABA: sulphonamides, Dapsone.

N.B: Dapsone: Bacteriostatic, good absorbed, entrohepatic cycle.

Use: Leprosy é rifampcin + clofazimine to avoid resistance. For 2 years.

b) ↓ dihydrofolate reductase: Trimethoprime and pyrimethemine.

2- ↓ DNA:-Some antiviral and anticancer. - Griseofulvine, flucytosine.

- Metronidazole and chloroquine. – Quinolones.

3- ↓ RNA: Rifampicine (↓h RNA polymerase).

Fluroquinolones (Direct)

Mechanism: ↓ DNAgyrase(subclass from topisomeraseII in G-ve) and IV in g+ve

→↓ supercoiling& replication of DNA→ bactericidal.

NB: topisomerase II present in mammalian cells.

Spectrum: broad Mainly gm – ve cocci and bacilli especially ciprofloxacin.

* Less than β lactms on gm +ve. Not anaerobic nor spirochetes.

Resistance: alterations in the target enzymes (DNA gyrase and topoisomerase IV) and changes in drug entry and efflux

Absorption: good. ↓ with antacids ,sucrlfate,Fe^{++}.

Distribution: extra + Intra + CSF (↓conc)

Excretion: renal (active). ↑t ½ → once daily. Blocked by probencid.

Classification:. *early non – flurinated:* Nalidixic acid, cinoxacin→

↓ systemic levels use: lower UTI only.

1st generation: ↑ gm-ve, moderate gm + ve

Ciprofloxacin, ofloxacin, Norfloxacin, Lomefloxacin,.

2nd generation ↑ gm –ve, ↑ gm + ve. Levofloxacin, Clinafloxacin

.***3rd generation:*** ↑ gm-ve, ↑↑ gm + ve, gatifloxacin, sparfloxacin

. ***4th generation***: ↑ gm-ve, ↑↑↑ gm + ve, anaerobics. Moxifloxacin,

Trovafloxacin (hepatotoxic so reserved for life threatening infections).

Uses:

1- 1st Choice in acute gastroenteritis caused by salmonella, shigella E. coli, and Helicobacter. Use: Ciprofloxacin(DOC in anthrax).

2- Urinary tract infection prostatitis, gonorrhoea and pseudomonas e.g ciprofloxacin.

3- Soft tissues, bones and joints, intra-abdominal and respiratory infection.

4- Prophylaxis infections in Neutropenic patients.

5- Eradication of meningococcal and salmonella carries.

Adverse effects:

1- CNS: insomnia, dizziness, convulsions. 2- GIT upsets.

3- Skin rash and photosensitivity, anaphylaxis, Nephrotoxic, crystaluria.

4- Drug interaction: Enzyme inhibition →↓ metabolism of theophylline.

Contraindications: 1- Pregnancy, lactation, 2- ↓ 18y. (arthropathy).

✳ Sulphonamides ✳

Mechanism : Compete with paraaminobenzoic acid (PABA) for dihydroptroate synnthetase →↓ DNA & RNA synthesis → No multiplication → Bacteriostatic.-

Antagonism: PABA- procaine – Pus.

N.B. : Human use preformed folic acid → not affected by sulphonamides.

Spectrum : All cocci, - ve Bacilli (Not salmonella) , chlamydia, protozoa.

But enhance growth of rickettsia and coxiella not in typhus or Q fever.

Resistance : 1- Over production of PABA, by bacteria.

2- Production of enzymes that inactivate drug.

3- Alternative metabolic pathway for folate synthesis.

Classification & absorption:

1- Good -absorbed from GIT:

a) Short acting (6h): sulphasoxszole (no acetylation ,soluble).

b) Intermediate: (12 h): Sulphamethoxazole(moderate acetylation).

*Sulphadiazine(more acetylation) + pyrimethamine in toxoplsmosis.

c) Long (1week) sulphadoxine é pyrimethamine in malaria,.

2- Poorly absorbed: kill intestinal flora → fungus ++ → superinfection. Sulphasalzine use ulcerative colitis, sulphaguanidine use, Bacillary dysentery.

3- Topical: sulphacetamide (eye drops), mafenide use wounds with Pus.

-silver sulfadiazine:less toxic than mafinide.

Distribution: extra cellular, intracellular, pass BBB.

Metabolism: In Liver by actylation (Partial).

Excretion:a) Free active —use→ UTI: sulphasoxazole, co-trimoxazole.

b) Acelylated: Crystalluria in acidic urine(sulphadiazine).

Use: as spectrum + Above. But resistant developed.

Adverse effects :

1- allergy : Photosensitivity, steven- Johnson syndrome: fever , rash,skin necrosis.

Also with:trimethoprim, penicillin,cefexime,barbiturates,phenytoin,lamotrigine

2- Crystalluria Ttt ↑ fluids, alkalization of urine, use soluble forms.

3-Blood dyscrasia (reversible):Aplastic anemia agranulcytosis, thrombocytopenia.

4- Haemolytic anemia (↓ G6 PD): more in children & black.

5- Kernicterus : displace bilirubin from PLPB → Pass BBB.

6- displace oral anticoagulants, sulphonylurea, phenytion →↑ action.

7- super infection (diarrhea): with poorly absorbed.8-Hepatotoic.

Contraindication: 1- ↓ 2M 2- pregnancy, lactation 3- ↑ creatinine

Co - Trimoxazole = sulphamethoxazole + Trimethoprim → Synergism

PABA dihydropetroate Folic acid dihydrofolic acid Reductase …RNA, DNA

1) Resistance less developed. 2) Bactericidal.

3) Used in typhoid fever. 4) Produce megaloblastic anaemia.

N.B$_1$ Antipseudomonal drugs : 1- Carboxypenicillins & ureidopenicillins.

2- 3rd,4th generation cephalosporins. 3- Monobactam: Aztreonam.

4- Tobramycin & amikacin,gentamycin. 5- Quinolones.

N.B$_2$: B. lactamse resistant drugs:

1- B-lactamase resistant penicillins. 2- Cephalosporins.

3- Carbapenems. 4- Monobactam. 5- Vancomycin.

6- Na fusidate. 7- Clindamycin. 8- Rifampcin.

N.B$_3$: Chloramphenicol, Tetracyclines, ↓ conc. Of macrolides, sulphonamides, dapsone,nitrofurantoin, clindamycin,lincomycin and trimethoprim are bactoriostatic, Others are cidal.

N.B$_4$: Alkaline urine increase activity of sulphonamides, aminoglycosides & macrolides.

Quinlones not affect by changes in urine PH.

Others are more active in acidic urine.

N.B_5 : Aminoglycosides, cephalosporins, tetracyclines are **nephrotoxic.**

N.B_6 :Serious **hepatotoxic** with Tetracyclines, Rifampicin, estolate ester of erythromycin, INH. ketoconazole, pyrazinamide:less serious.

N.B_7:Tttof anthrax:ciprofloxacin(DOC),doxycycline(2^{nd} choice), rifampcin, vancomycin, imipenem, chloramphenicol, ampicillin, clindamycin, clarithromycin.

N.B_8:Drugs with disulfiram-like action:Moxalactam,cefoprazone, metronidazole, ,chloropropamide.

Drug in urinary tract infections (UTI)

I Sulphonamides,trimethoprim, penicillin, cephalosporins, aminoglycosides, Quinolones (in low doses)

II Urinary antiseptics : rapid excretion →↓ systemic activity.

1-Nitrofurantoin : First choice in lower UTI while in upper UTI (Acute pyelonephritis)**cefalexin** is first choice.

Mechanism: ↓DNA.Static in ↓dose ,cidal in ↑ on gm +ve and –ve bacteria.

Side effects: * Neuropathy *Idioncyncrasy: Haemolysis (↓ G_6PD).

*N and V. *Brown urine. *Hepatitis.

2-Fosomycin: ↓1^{st} step cell wall synthesis. Broad. Cidal .Single dose in LUTI.

3- Nalidxic acid : non-fluorinated quinolone. Affect (G-ve).Antagonism with 1

4- Methenamine: affect (G-ve): Not with sulpha, release formaldhyde in ↓ pH.

5- cyclosporin : ↓ cell wall. * CNS : tremors, psychosis.

6- Acidifying agents e.g. mandelic acid (antiseptic), ammonium chloride.

Anti-tubercles drugs

I - First line drugs : All good absorbed oral except streptomycin IM.

1- Isoniazid (INH) : Ttt & prophylaxis. Most effective.

Mechanism: ↓ Mycolic acid synthesis → loss of integrity of mycobacteria wall → Bactericidal in dividing & static in resting bacteria.

Distribution: extra, intracellular + C.S.F.

Metabolism :by acetylation (like procainamide hydralazine,sulfonamides).

Adverse effects :

1-Peripheral neuritis give pyridoxine (B6). Insomnie, convulsions.

2-Hepatitis :Unlike those of CNS more in rapid acetylators & alcoholics.

3-Allergy. 4-Haemolysis (↓ G_6PD).

5- ↓metabolism of phenytoin, carbamzepine and warfarin.

2- Rifampicin (Rimactane) :

Mechanism: Inhibit DNA-dependant RNA polymerase (Not in human) →↓ RNA synthesis, bactericidal.

Spectrum: Broad including virus, chlamydia .

Distribution:extra, intracellular + C.S.F. **Metabolism**: liver.

Excreation: Enterohepatic cycle, excreted in bile, urine.

Uses :

1- T.B. 2- Prophylactic in H. influenza type B.

3- Prophylactic in meningiococcal meningitis (the best drug).

4- Staph endocarditis with penicillin . 5- With dapsone in leprosy.

Adverse effects :

1- hepatotoxic. 2- Proteinuria. 3- Ataxia, confusion.

4- colors secretions Red e.g. urine (harmless).

5- Influenza-like picture ; if intermittent course is used.

6- enzyme inducer : ↑ oral anticoagulant & contraceptives metabolism.

3- Ethambutol : Produce visual toxicity e.g. optic neuritis.

Use : in resistant strains. é INH + Rifampicin.

4- Pyrazinamide : Hepatotoxic ; ↓ uric acid excretion. Short term.

5- Streptomycin : In T.B. Bacteriostatic. * ↓effect→↓ use.

II- 2nd line drugs (↑toxicity) : cycloserine, paraaminosaliaylic acid, ethionamide, kanamycin, Amikacin,capromycin,flouroqinolones,rifabutin

N.B$_1$: If one drug alone →↑ toxicity, rapid resistance (No cross resistance) → A drug combination is used e.g. isoniazid + Rifampicin + pyrazinmide for 2M. then izoniazide + Rifampicin for 4M.

N. B$_2$: T.B é pregnancy or renal failure → INH + Ethambutol

Anti - malarial durgs "oral"

I- Prophylaxis in endemic areas : Needs → primary tissue schizonticide (causal prophylaxis) affect primary exoerthrocytic stage. e.g., **Proguanil, pyrimethamine ; chloroquine.** → megaloblastic anemia: give folinic

* **Mechanism** : ↓ Dihydrofolic acid reductase →↓ Folic a.

II- Treatment of acute attack clinical cure :

Needs → blood schizonticide → CloroQuine (I.M. in severe cases)

Adverse effects : 1- Hoemolysis (↓ G6PD). 2- ↓Bl.P. 3- Blurred vision.

4- Heart - - 5- Bone marrow inhibition. 6- teratogenic

7- psychological disorder. 8- nail, hair loss.

Uses :

1- Acute attack of malaria + causal prophylaxis.

2- Amoebic hepatitis, (1st choice) liver abscess 3- Girdiasis.

4- Lupus erthymatosis, rheumatoid arthritis (immunosuppressive).

III- anti - relapse (radical cure):

* Needs → secondary tissue schizonticide to affect secondary exoerthrocytic stage, e.g., **Primaquine.** Affect plasmodium mitochondria

Affect also Gametocites of all spices.

Adverse effect : 1- Hemolytic anemia (↓G_6PD). 2- methemoglobinemia.

3- e` proguanil → ↓ metabolism → ↑ toxicity.

Anti - amoebic drugs

I - Tissue amoebicides : Mainly against trophozoites.

1- Metronidazole (Flagyl) oral, iv : (Drug of choice) cidal – **Tinidazole**

Effective in all forms put less on cysts + trichomoniasis +Giardiasis + Gardnella anaerobic infections + peptic ulcer due to helicobacter + prophylactic before GIT surgery + antibiotic induced diarrhea. (pseudomempranous colitis), ulcerative gingivitis, radiosenstizer, balantidium, coli (if tetracycline failed).

Adverse effects : 1- Disulfiram- Like effect. 2- carcinogenic, teratogenic.

3-Peripheral neuritis. 4- GIT disturbance. 5- leucopenia.6-Red urine

7-Metallic taste. * Reduce dose in liver disease.

2- Ipecacuanha alkaloid : Emetine, dehydroemetine (im) :

* **Use :** sever intestinal, hepatic amoebiasis & fasciola hepatica.

* GIT, Nephro, CVS, NM toxicity → limit use.

3- Cholorquine : ↑ liver conc., use hepatic amoebiasis.

II - Luminal amobicides : oral

1- Diloxanide : Against cysts only use Asymptomatic cases (best drug).

* Used é metronidazole in intestinal & hepatic forms → best results.

Adverse effects : 1- GIT disturbance: flatulence. 2- Proteinuria.

3- Allergy 4- Not in pregnancy or infants.

2- Halogenated hydroxyquinoline e.g. Diiodohydroxyquin, diodoquine, vioform.

* Against trophozoite & cyst. * Poor absorption.

Adverse effect : 1- Neurotoxicity (SMON) 2- Hepatotoxic .

3- Paromomycin : * Aminoglycoside. * Not absorbed. *Cidal

4- tetracycline →↓ flora→ starvation of amoeba → indirect cidal.

Anti- fungal Drugs

Mechanism : All ↓ cell membrane function (↓ synthesis of ergosterol) →↑permeability EXCEPT griseofluvin and flucytosine which inhibit DNA synthesis the later converted to 5. Fluorouracil in fungi.

I- Drugs in superficial fungal infection:

1- Nystatin (oral, ointment) use candidiasis (moniliasis) superinfection.

2- Allyamines: Terbinafine, naftifine (topical) use dermatophytes e.g. tinea pedis.

II- Drugs in systemic fungal infection:

1- Griseofulvin (oral) static * Absorbed from GIT * enzyme inducer.

Use: ring worm scalp, skin, nail & hair mycotic diseases, athlete foot.

2- Amphotercin B : * iv → systemic (most potent) * Oral → local on GIT.

Side effects : Nephrotoxic , allergy, fever, GIT upsets.

3- Flucytosine (oral) : * ↑ Absorption * Distribution : All tissues.

Use : é amphotercin to ↑ effect, ↓ toxicity & resistance (not alone)

Side effect: * Alopecia * Hepatotoxic * GIT upsets.

4- Azoles : Broad spectrum.

a- Ketoconazole (oral) * ↓ PH →↑ absorption * ↑ distribution (Not CSF).

* Slow onset. * Hepatotoxic * antiandrogenic * enzyme inhibitor.

↓ synthesis of steroid hormones use cushing.

b- Itraconazole (oral) * ↓ PH →↑ absorption * Enzyme inhibitor.

Side effect : ↑ Dysrhythemia of terfenadine * GIT upset.

c- Fluconazole (oral, iv) : * ↑ bioavailability * Distribution : all tissues.

Less toxic than amphotercin , flucytosine, ketoconazole.

d- Miconazole and clotrimazole : topical, if iv →↑ toxicity.

Use : Ring worm, vulvovaginal candidiasis.

Adverse effect : * Allergy. * GIT upset. * Dysrhythemia. * thrombophlebitis.

Antiviral Drugs

I- inhibition of nucleic acid sythesis:

1- Acyclovir (zovirax): oral/ IV./ topical in herpes simplex and zoster.

2- idoxuridine, vidarabin: topically in herpes simplex.

3- Ribavarin: aerosol for respiratory viruses.

4- Zidovudine: orally in AIDS. ↓ viral reserve transcriptase

II- inhibition of Penetration to host cells:

1- Gamma globulins: IM. To prevent measles, infective hepatitis.

2- Amantadine: Orally in prophylaxis of influenza A and antiparkinsonil.

III- inhibition of late protein synthesis: methisazone in small pox.

IV- Inhibition of Assembly or Release of viral particles: Rifampicin.

IIV- Immunomodulators: **Human interferons**: inhibit viral replication.

- SC. In chronic active hepatitis B and C.

Side effects: alopecia, bone marrow depression, anorexia and influenza like.

For hepatitis c: -Sofosbuvir+Ledipasvir(12-24 weeks)

For HIV: -Bictegravir+Tenofovir+Emtristabine(ffor life)