Toxicity of Metals

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* Although some metals are necessary in biological systems, they are usually required only in trace amounts, and even essential metals in excess can be toxic.
* Metals are known to generate free radicals, which may result in membrane and organelle degradation.
* Metals are also known to combine with normally occurring molecules, such as proteins, and inhibit or alter their activity.
* The chelator may have one or more binding sites for the metals and its affinity for a particular metal vary with its structure and the properties of the metal.
* The chelator-metal complex must be excreted from the body without causing additional toxicity.

* DIMER CAPROL:

Dimercaprol 2,3-dimereapto-1-propanol, British anti-Lewisite, BAL)is an effective chelating agent for metals such as As, inorganic Hg, Bi, Cd, Cr. Co, Ni, Sb and Au.

These metals form strong bonds with sulfur atoms in this compound. Once the metal is chelated, it is unable to enter the cell and may be excreted from the body.

* Ethylene Diamine Tetra Acetic Acid (EDTA)

Is forms four or six bonds with metal ions and forms chelates EDTA is used as an anticoagulant.

The Ca salt of EDTA is the chelator of choice for Pb toxicity:

Ca disodium EDTA exchanges its chelated Ca for Pb, and resulting Pb chelate is rapidly excreted in the urine.

i.v. Ca disodium EDTA is also used in Cd and Fe poisoning.

Ca EDTA should be administered only when if it is necessary.

* PENICILLAMINE :

(cuprimine) is a chelating agent for Hg, Pb, Fe, and Cu. Penicillamine forms soluble complexes and decrease the toxic levels of the metals. It is well absorbed from the GI tract and excreted in urine. Food decrease the absorption of penicillamine over 50% It should not be used in patients who are allergic to penicillin.

* DEFEROXAMINE

Deferoxamine is an Al and Fe(II) chelator that has been used in the treatment of acute Fe poisoning and chronic Fe or aluminum overload. It is not effective orally and requires prolonged subcutaneous injection to achieve efficient Fe excretion

* SUCCIMER:

Succimer (dimercaptosuccinic acid, DMSA) and dimercaptopropanesulfonate DMPS) are used in the treatment of Pb poisoning to remove excess Pb from the body, especially in children.

It is also under investigation as a treatment of Hg poisoning due to dental fillings.

In healthy individuals approximately 20% of an oral dose of DMSA is absorbed from the GI tract.

* ARSENIC (As):

Organic forms of As are usually less toxic than inorganic forms. Some organic forms of As are gaseous or low- boiling liquids at normal temperature.

When As burns or gets in contact with acids arsine gas (deadly gas) is very poisonous.

1- Inorganic As : is found in ground water surface water and food e.g rice and grains) Arsenic trioxide (As203) is a major ingredient of traditional. Chinese medicine is used against acute promyelocytic leukemia. Fowler's solution (potassium arsenite) had been used as a treatment for asthmatic patients. *inhalation of inorganic* As increases the risk of lung cancer.

* Inorganic As compounds mainly used in wood

preservatives, insecticides, herbicides, and in the production of metal alloys.

The toxicity of As is dependent on:

* the chemical form and the oxidation state at the time of exposure
* The physical state (gas, solution, powder particle size), the rate of absorption into cells, elimination rate determine the toxic nature.
* Inorganic pentavalent As does not directly react with the active sites of enzyme systems. It first reduces to trivalent As, then binds to -SH and -OH groups and interferes with enzyme activity
* Inactivation of pyruvate dehydrogenase with trivalent As will prevent the generation of adenosine -5-triphosphate (ATP).

* Arsenic inhibits succinic dehydrogenase and can uncouple oxidative phosphorylation, a process that results in disruption cellular functions.
* Glutathion and other thiols act as reducing agents in these reactions. In mammals the liver is an important site of As methylation. Arsenic is also methylated in other tissues such as testes, kidney, liver, and lung.
* SYMPTOMS of ACUTE TOXICITY:

Patient with acute exposure show GI distress characterized by nausea, vomiting, abdominal pain, and profuse watery or bloody diarhea, Death is common in patients that have ingested large doses.

* Respiratory effects such as pulmonary distress are hemorrhagic bronchitis and respiratory seen with acute oral poisoning.

* Common effects of acute As poisoning are: Hypotension, Tachycardia, Metallic taste in the mouth, Garlic odor in the breath, Delirium, Anemia and leukopenia.

SYMPTOMS of CHRONIC TOXICITY :

Chronic toxicity is characterized by changes in skin pigmentation, plantar and palmar hyperkeratosis, Gl symptoms, anemia, skin cancers, and liver disease.

TREATMENT of ACUTE POISONING:

* Prevention or delay of As absorption in cases of oral high-dose exposure may be done by consumption of large volumes of water, gastric lavage, or cathartics initiated within a few hours of exposure.
* Chelation therapy with BAL and D-penicillamine is indicated for acute As poisoning. Chronic As poisoned patients who are symptomatic may be removed from the source of exposure without chelation therapy.

* CADMIUM :

sources of cadmium in the environment include the release of Cd used in; Electroplating , Pigments (Cd selenide), Solders , Nickel-cadmium batteries (Cd sulfide) , plastic stabilizers

* Most Cd enters the environment through coal burning, waste incineration, metal mining and smelting, and from the use phosphate fertilizers.
* Exposure to the general population occurs through cigarette smoke, food consumption, drinking water, and incidental ingestion of soil. For nonsmokers food is the largest nonoccupational source.
* Root vegetables such as potatoes may pick up more Cd and the grains contain can concentrate Cd. Seafood, particularly crustaceans, such as crab and lobster have higher Cd levels.

* Coffee and tea may contain significant cadmium levels.
* Absorption of Cd varies considerably by the route of exposure. Only about 5% of an ingested dose of Cd is absorbed from the Gl tract but absorption from the lung is as high as 90% Cd clears rapidly from the blood and concentrate in various tissues such as liver and kidney. Biological half-life is around 30 years.
* Liver is the primary target in acute Cd exposure Hepatocellular necrosis with infiltration by inflammatory cells has been seen.
* cadmium was classified as a human Carcinogen. occupational exposure is associated with lung and prostate cancers, although the carcinogenic mechanism is not known.
* Cd does not form stable DNA adducts but stimulates cell

* proliferation and inhibits DNA repair.

SYMPTOMS of ACUTE TOXICITY:

* Heating of Cd and its compounds to high temperatures produces Cd oxide fumes, which upon inhalation cause flu-like symptoms (metal fume fever). The condition is benign and the treatment is symptomatic. More severe exposures may cause lung damage and fatality.
* Cadmium oxide fume is a severe pulmonary irritant. Cd dust is a less potent irritant than Cd fume. Inhalation of fumes with a high Cd concentration has been responsible for fatalities.
* Pulmonary symptoms and clinical signs reflect lesions ranging from nasopharyngeal and bronchial irritation to pulmonary edema and death.

* other possible signs and symptoms are: headache, muscle aches, nausea, vomiting, and diarrhea.
* Respiratory symptoms linger for several weeks, and impairment of pulmonary function persists for months.

SYMPTOMS of CHRONIC TOXICITY :

Chronic exposure to Cd affects the kidney, lungs, and bone

* In kidney, chronic exposure is implicated in the development of cancer.
* In lungs, long-term inhalation results in decreased lung friction and emphysema.
* Although oral is low, chronic exposure to high levels of Cd in food causes bone disorders(osteoporosis, osteomalacia) long-term ingestion of water and food contaminated with Cd was associated with a crippling condition itai-itai' (ouch-ouch) disease.

* Other consequences of Cd exposure are:

Anemia , yellow discoloration of the teeth, rhinitis, occasional ulceration of the nasal septum, damage to the olfactory nerve, loss of the sense of smell (anosmia)

TREATMENT:

Calcium Disodium EDTA may be used in the treatment of the acute intoxication but care must be taken in the presence of renal impairment.

High intake of zinc as well as selenium will protect against further Cd absorption, and adequate body levels of zinc may displace some tissue Cd.

iron copper, selenium, and vitamin C have been shown to increase Cd elimination as well as can be measured by urine levels. No chelating agent can be proposed for the treatment of the chronic intoxication.

LEAD:

* Lead (Pb) is one of the oldest metal known and it was used by the ancient Babylonians Egyptians, and the Romans to make water pipes and solder. The main use of Pb is in the production of storage batteries and in sheathing electric cables. It is also useful as protective shielding from X-rays and radiation from nuclear reactors.
* Lead compounds are commonly used as pigments in paint, putty, and ceramic and as insecticides Lead toxicity affects virtually all organs and systems of the body.
* Sources of occupational Pb exposure are lead mining, refining, smelting., battery manufacturers, gas station attendants, pipe fitters, glass manufacturers, shipbuilders and construction workers

* lead poisoning results from the interaction of the metal with groups, biological electron-donor groups, such as the sulfhydryl groups, amine, phosphate, and carboxyl groups.
* lead interacts with essential cations, particularly calcium, iron, and zinc; it interferes with Na+/ K+ ATP pump.
* Lead interferes with heme biosynthesis by interfering with ferrochelatase (aminolevulinic acid synthetase ALAS and ALAD (aminolevulinic acid dehydrase).
* In the nervous system. Pb substitutes for Ca as a secondary messenger in neurons. Blocking voltage-gated Ca channels, inhibiting influx of Ca and subsequent release of neurotransmitter. result is an inhibition of synaptic transmissions.
* **The central nervous system appears to be affected the greatest by lead. Lead peripheral neuropathy leads to loss of wrist extensors.**

* Children in particular are susceptible to its devastating effects on mental development and intelligence.
* Blood Pb concentrations of 20-25ug dl can cause irreversible CNS damage in children.
* Following ingestion, Pb is distributed widely to plasma and soft tissue and redistributes and accumulates in bone.
* In children, bone Pb accounts for about 73% of the to total body burden, while in adults it increases 94% due to the slower turnover rate of bone with age.
* Lead is excreted primarily by the kidneys as soluble salts or through biliary clearance in the GI tract in the form of conjugates with organic compounds.
* Exhalation is also considered to be a major excretion route of organic Pb.
* Blood Pb is found primarily in RBCs (99%) distribution

occurs primarily to soft tissues. Liver, lung, spleen, and kidneys have the highest concentration, with redistribution resulting in high bone concentrations.

* Organic Pb is metabolized in the liver by an oxidative dealkylation reaction catalyzed by cytochrome P450.

SYMPTOMS of ACUTE TOXICITY:

* Exposure to excessive Pb through the GI tract or by inhalation, usually results in cramping, colicky abdominal pain, and constipation.
* Severe abdominal pain is accompanied by nausea, vomiting, and bloody stools. Early symptoms of Pb exposure include fatigue, apathy, and vague GI pain.
* Headache, confusion, coma, seizures and optic neuritis are all manifestations of Pb neurotoxicity.
* Upon further exposure, central nervous system symptoms,

such as insomnia, confusion, impaired concentration, and memory problems become more pronounced.

* Lengthy exposure can present with a distal motor neuropathy, progressing to Pb encephalopathy with seizures and coma.
* Reproductive problems, such as infertility in man, spontaneous abortions have been reported. Clinical Pb poisoning is called (PLUMBISM)
* SYMPTOMS of CHRONIC TOXICITY :

Chronically exposed individuals develop anemia and demonstrate pallor. Jaundice may be seen due to acute hemolysis. Examination of the gums may show a blue- gray pigmentation, or 'lead-line'

TREATMENT of ACUTE POISONING:

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* Parenteral administration of chelating agents dimercaprol. and CaNa2-EDTA, is used to reduce body burdens of absorbed Pb
* Penicillamine has been used as an oral chelating agent, although it is not as effective as EDTA.
* EDTA mobilizes Pb from bone to soft tissue and may aggravate acute toxicity if not given in conjunction with dimercaprol.
* Succimer is the only FDA-approved orally administered chelating agent for treating children with Pb blood levels 45ug/dl