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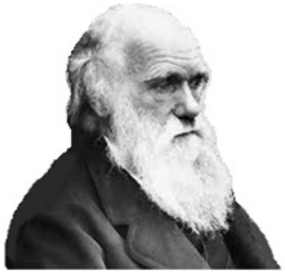

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Heavy metal toxicity - metabolism, absorption, distribution, excretion and mechanism of toxicity for each of the metals

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ABSTRACT

The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury and arsenic. These metals have been extensively studied and their effects on human health regularly reviewed by international bodies such as the WHO. Heavy metals have been used by humans for thousands of years. Although several adverse health effects of heavy metals have been known for a long time, exposure to heavy metals continues, and is even increasing in some parts of the world, in particular, in less developed countries. However, over the last 100 years, emissions have declined in most developed countries. Cadmium compounds, the exception, are currently mainly used in re-chargeable nickel-cadmium batteries. Cadmium emissions have increased dramatically during the 20th century, one reason being that cadmium-containing products are rarely re-cycled, but often dumped together with household waste. Cigarette smoking is a major source of cadmium exposure. In non-smokers, food is the most important source of cadmium exposure. Recent data indicate that adverse health effects of cadmium exposure may occur at lower exposure levels than previously anticipated, primarily in the form of kidney damage, but possibly also in bone effects and fractures. Many individuals in Europe already exceed the recommended exposure levels and the margin is very narrow for large groups. Therefore, measures should be taken to reduce cadmium exposure in the general population in order to minimize the risk of adverse health effects. The general population is primarily exposed to mercury via food, fish being a major source of methyl mercury exposure, as is dental amalgam. The general population, however, does not face a significant health risk from methyl mercury, although certain groups with high fish consumption may attain blood levels associated with a low risk of neurological damage to adults. Since there is a risk to the fetus in particular, pregnant women should avoid a high intake of certain fish, such as shark, swordfish and tuna; fish (such as pike, walleye and bass) taken from polluted fresh waters should especially be avoided. There has been a debate on the safety of dental amalgams and claims have been made that mercury from amalgam

may cause a variety of diseases. However, there are no studies so far that have been able to show any associations between amalgam fillings and ill health. The general population is exposed to lead from air and food in roughly equal proportions. During the last century, lead emissions to ambient air caused considerable pollution, mainly due to lead emissions from petrol. Children are particularly susceptible to lead exposure due to high gastrointestinal uptake and the permeable blood-brain barrier. Blood levels in children should be reduced below the levels so far considered acceptable as recent data indicates that lead may hold neurotoxic effects at lower levels of exposure than previously anticipated. Although lead in petrol has dramatically decreased over the last decades, thereby reducing environmental exposure, phasing out any remaining uses of lead additives in motor fuels should be encouraged. The use of lead-based paints should also be abandoned, and lead should not be used in food containers. In particular, the public should be aware of glazed food containers, which may leach lead into food. Exposure to arsenic is mainly via intake of food and drinking water, food being the most important source in most populations. Long-term exposure to arsenic in drinking water is mainly related to increased risks of skin cancer, but also enhanced risk of some other cancers, as well as other skin lesions such as hyperkeratosis and pigmentation changes. Occupational exposure to arsenic, primarily by inhalation, is causally associated with lung cancer. Clear exposure-response relationships and high risks have been observed.

Keywords: Heavy metals, nutrients, proteins, uptake, growth, Fe, Cu, Pb, Cd, Hg, Ni, Zn

1. METALS AND DRUGS (CHELATORS) TO CONSIDER

METAL	CHELATING AGENTS (DRUGS)
Lead	Ethylenediamine-tetraacetic acid (EDTA) 2,3-dimercaptosuccinic Acid (Succimer) 2,3-dimercaptopropanol (BAL, Dimercaprol) Penicillamine
Cadmium	Ethylenediamine-tetraacetic Acid (EDTA)
Mercury	N-acetyl-penicillamine (NAP) Penicillamine 2,3-dimercaptopropanol (BAL, Dimercaprol) 2,3-dimercaptosuccinic Acid (Succimer)
Arsenic	N-acetyl-penicillamine (NAP)

Antimony	Ethylenediamine-tetraacetic acid (EDTA)
Iron	Deferoxamine

2. HEAVY METALS AND ANTIDOTES METALS

Lead (Pb)

1. Absorption

- Skin: alkyl lead compounds, because of lipid solubility (methyl and tetraethyl lead)
- Inhalation: up to 90% depending upon particle size GI: adults 5 to 10%, children 40%

2. Distribution

Initially carried in red cells and distributed to soft tissues (kidney and liver); redistributed to bone, teeth and hair mostly as a phosphate salt. Rates of absorption and distribution are greatly influenced by dietary intake and body stores of phosphate, calcium and iron relative to lead

- high PO_4, Pb storage in bone
  - high Vitamin D, Pb storage in soft tissue
- low PO_4, Pb sequestered in soft tissue
- high Ca^{2+}, Pb sequestered in soft tissue

3. Half-life in blood 30-60 days, bone 20-30 years 3. Sources of exposure

- GI - paint, pottery, moonshine
- Inhalation - metal fumes
- Skin -tetraethyl lead in gasoline

4. Mechanisms of toxicity

- Inhibition of heme biosynthesis (see figure 1). Heme is the essential structural component of hemoglobin, myoglobin and cytochromes.
- Binds to sulfhydryl groups (-SH groups) of proteins

5. Diagnosis

(1) History of exposure
(2) Whole blood lead level
- Children: >25µg/dl treatments
- Adults: >50 µg/dl candidates for treatment; > 80 µg/dl & symptomatic, treatment initiated, >120 µg/dl encephalopathy

(3) Protoporphyrin levels in erythrocytes are usually elevated with leadlevels > 40 µg/dl
(4) Urinary lead excretion >80 µg/dl
(5) Urinary delta aminolevulonic acid () ALA)

(6) Lead mobilization test (redistribution toxicity)

6. Symptoms

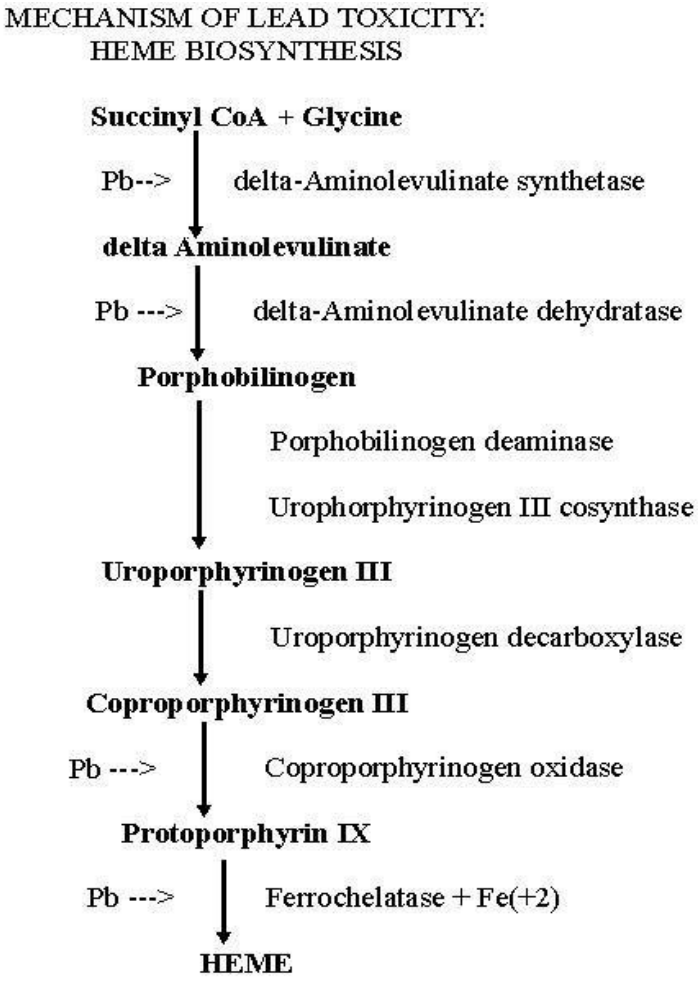
(1) Acute - nausea, vomiting, thirst, diarrhea/constipation, abdominal pain, hemoglobinuria, oliguria leading to hypovolemic shock
(2) Chronic -

- GI: lead colic (nausea, vomiting, abdominal pain)
- NMJ: lead palsy (fatigue, wrist-drop)
- CNS: lead encephalopathy (headache, vertigo, irritation, insomnia, CNS edema

7. Treatment

(1) Remove from exposure
(2) $CaNa_2EDTA$
(3) 2,3-dimercaptopropanol (Dimercaprol, BAL)
(4) 2,3-dimercaptosuccinic acid (Succimer)
(5) D-penicillamine

Figure 1.



Cadmium (Cd)

1. Absorption

(1) Inhalation 10 to 40%
(2) GI 1.5 to 5%

2. Distribution: initially bound to albumin and blood cells; subsequently bound tometallothionnin in liver and kidney tissue. Half life 10-20 years

3. Sources of exposure

(1) GI - pigments, polishes, antique toys.
(2) Environmental- electroplating, galvanization, plastics, batteries
(3)Inhalation industrial, metal fumes, tobacco - 1-2 µg/pack

4. Mechanisms of toxicity

(1)Inhalation: lung - local irritation and inhibition of $alpha_1$antitrypsin associated with emphysema
(2)Oral: kidney-proximal tubular injury (proteinuria) associated with$beta_2$-macroglobulin

5. Diagnosis

(1) History of exposure
(2) whole blood cadmium level >80 µg/dl

6. Symptoms

a. Acute
- oral: vomiting, diarrhea, abdominal cramps
- inhalation: chest pains, nausea, dizziness, diarrhea, pulmonary edema

b. Chronic
- oral: nephrotoxicity
- inhalation: emphysema-like syndrome and nephrotoxicity

7. Treatment

(1) Remove from exposure

(2) $CaNa_2EDTA$

(3) **2,3 dimercaptopropanol (BAL) Cadmium complex is extremelynephrotoxic and therefore is not used**

Mercury (Hg)

1. Absorption

(1) GI: inorganic salts are variably absorbed (10%) but may be convertedto organic mercury (methyl and ethyl in the gut by bacteria), organic compounds are well absorbed >90%
(2) Inhalation: elemental Hg completely absorbed

2. Distribution depends upon sources of exposure

Elemental Hg (vapor) crosses membranes well and rapidly moves from the lung to the CNS. Organic salts (lipid soluble) are evenly distributed, intestinal (intracellular)-fecal elimination. Inorganic salts concentrate in blood, plasma and kidney (renal elimination). Half life is 60 to 70 days.

3. Sources of exposure

(1) environmental from electronics and plastic industry
(2) seed fungicide treatment, dentistry

4. Mechanisms of toxicity

(1) dissociation of salts precipitates proteins and destroys mucosal membranes
(2) necrosis of proximal tubular epithelium
(3) inhibition of sulfhydryl (-SH) group containing enzymes

5. Diagnosis

(1) History of exposure
(2) Blood mercury

6. Symptoms

(1) Acute
(a) (inorganic salts) degradation of mucosa-GI pain, vomiting,diuresis, anemia, hypovolemic shock, renal toxicity.
(b) (organic) CNS involvement- vision, depression, irritability,blushing, intention tremors, insomnia, fatigue, diuresis.
(2) Chronic: CNS symptoms similar to acute organic poisoning withgingivitis, tachycardia, goiter, increased urinary Hg.

7. Treatment

(1) Remove from exposure
(2) Hg and Hg salts > 4 µg/dl : 2,3-dimercaptopropanol (BAL), $,$-dimethyl cysteine (penicillamine), most effective is N-acetyl-$,$-dimethyl cysteine (N-acetyl-penicillamine)
(3) Methyl Hg- supportive treatment (nonabsorbable thiol resins can begiven orally to reduce methyl Hg level in the gut).

Arsenic, As^{3+}, As^{5+}

1. Absorption

(1) GI inorganic: trivalent and pentavalent salts >90%. organic: also bound as tri and pentavalent >90%
(2) Inhalation: uptake is dependent upon particle size
2. Distribution accumulates in lung, heart, kidney, liver, muscle and neural tissue. Concentrates in skin, nails and hair. Half life is 7 to 10 hours.

3. Sources of exposure

(1) GI - well water, food. Environmental: by-product of smelting ore, AsGa in semiconductors, herbicides and pesticides
(2) Inhalation - fumes and dust from smelting

4. Mechanisms of toxicity

(1) Membranes: protein damage of capillary endothelium increasedvascular permeability leading to vasodilation and vascular collapse
(2) Inhibition of sulfhydryl group containing enzymes
(3) Inhibition of anaerobic and oxidative phosphorylation (substitutes forinorganic phosphate in synthesis of high-energy phosphates)

5. Diagnosis

(1) History of exposure
(2) Blood and urinary levels (acute)
(3) Hair or fingernail (chronic)

6. Symptoms

(1) Acute - damage to mucosa, sloughing, hypovolemic shock, fever, GIdiscomport/pain, anorexia
(2) Chronic - weakness, GI, hepatomegaly (jaundice > cirrhosis),melanosis, arrhythmias, peripheral neuropathy, peripheral vascular disease (blackfoot disease)
(3) Carcinogenicity - epidemiologic evidence; liver angiosarcoma, skinand lung cancer

7. Treatment

(1) Remove from exposure
(2) Acute: supportive therapy: fluid, electrolyte replacement, bloodpressure support (dopamine)
(3) Chronic: penicillamine w/o dialysis
❖ Arsine gas (AsH_3) acts as a hemolytic agent with secondary to renal failure.
❖ supportive therapy: transfusion; **(chelators have not been shown to be beneficial**)

Antimony

1. Absorption

❖ skin, inhalation and GI
❖ Ceramics, batteries, toys, drugs (organic antimonials)

2. Mechanisms

Inhibition of SH-group containing enzymes and substrate phosphorylation

3. Diagnosis and Symptoms - same as for Arsenic

4. Treatment

(1) Remove from exposure
(2) BAL & penicillamine, EDTA
(3) Stibine gas (SbH_3) is a hemolytic agent-supportive treatment

3. CHELATING AGENTS

Chelation is the formation of a metal ion complex in which the metal ion is associated with a charged or uncharged electron donor referred to as a ligand. It usually attaches or coordinates using one, two or more electron pair donor atoms (oxygen, nitrogen and sulfur).

A. Requirements for the ideal chelating agent

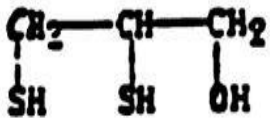
1. the compound should be soluble in aqueous medium
2. the chelating agent should be stable in the circulation
3. if it is given orally, it should be absorbed by the GI tract and it should be cleared by the kidney
4. the compound should be active at physiological pH
5. the compounds should chelate only the specific metals
6. the chelator itself should not be toxic
7. the chelator-metal complex should be less toxic than the metal alone

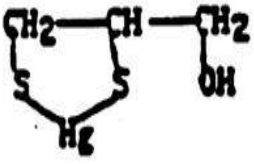
B. Chelators

1. 2,3-dimercatopropanol (dimercaprol) also known as British Anti Lewisite (BAL)-given IM in peanut oil

a. Structure

Isolated





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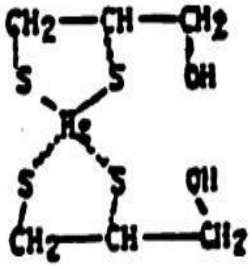


b. Use: arsenic, mercury, antimony, lead, gold, zinc, bismuth. Half life is less than onehour.

c. Toxicity:

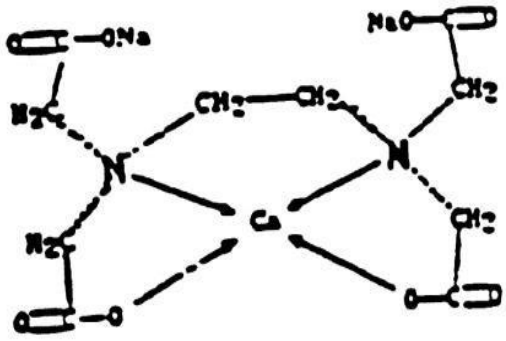
- CNS convulsions in high dose, given Q4H (i.e., given every 4 hrs)
- Increased Blood pressure (50 mm Hg) due to tachycardia and peripheral constriction of arterioles.
- Renal toxicity can be reduced by alkalizing the urine, which protects against dissociation of the metal-BAL complex. Toxicity is 50%

❖ Anxiety
❖ increased blood pressure
❖ nausea, vomiting and headache
❖ 1/3 of children treated react with fever

2. Ethylene diamine-tetraacetic acid (EDTA) given IV as the Calcium disodium salt. a.

Structure

Isolated



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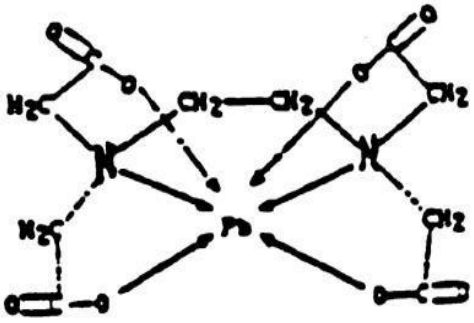


b. Uses

❖ Disodium EDTA binds calcium in blood to prevent clotting- used in blood collection and storage ii. chelator for lead

❖ only chelates circulating metal because EDTA cannot enter inside the cellmembrane

❖ frequently used in combination with BAL or penicillamine for treatment oflead poisoning

c. Toxicity

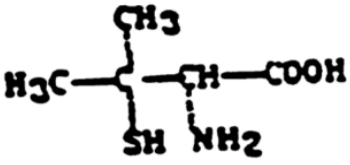
❖ tubular destruction due to release of metal or the metal-EDTA complex in thekidney.

❖ thrombophlebitis in some cases- too rapid infusion

d. d-isomer of beta,beta-dimethylcysteine (Penicillamine) given orally

a. Structure

Isolated



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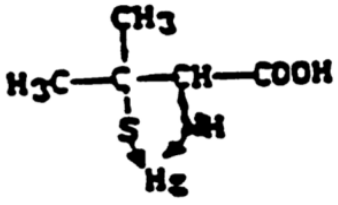
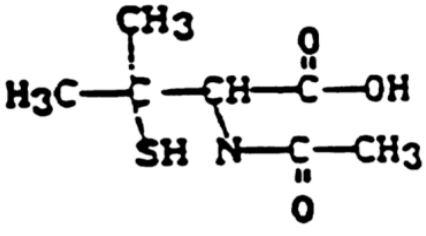
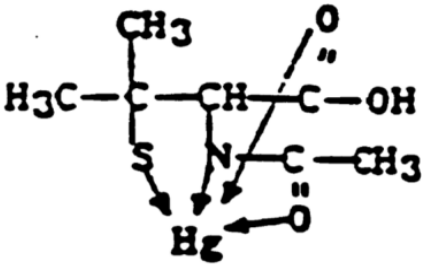


N-acetyl penicillamine





b. Uses lead, mercury, arsenic

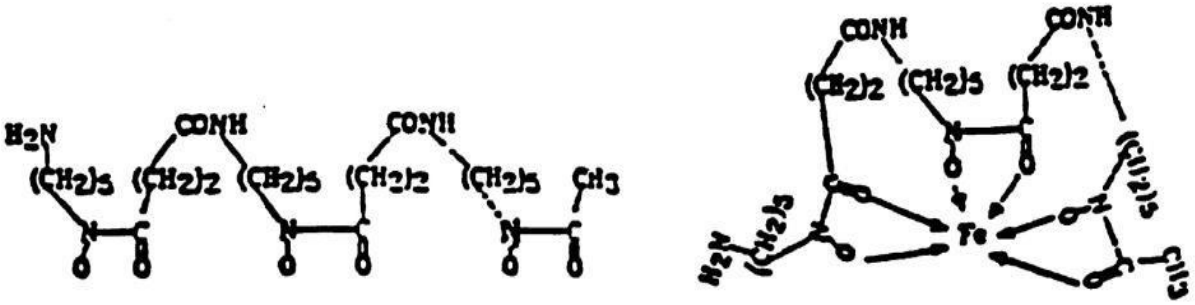
❖ copper - Wilson's disease (reduced or monovalent copper is elevated)c. Toxicity

❖ l-isomer depletes pyridoxine (Vitamin B_6), therefore d-isomer is used clinically ii. fever, skin rashes, leukopenia, nausea, vomiting
❖ anaphylactic reactions (do not use in the case of allergic to penicillin)

e. Deferoxamine

a. Structure

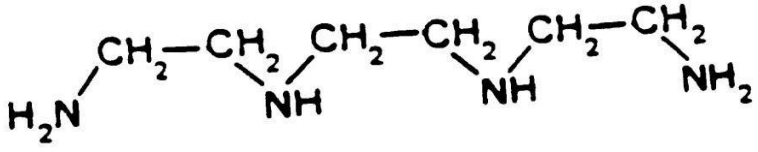
Isolated Complexed



b. Uses: iron (Fe^{3+}) poisoning IM or slow IV. It has also been used orally to chelate iron poisoning
c. Toxicity
❖ skin rash
❖ histamine release with reduced blood pressure (shock)iii. cataracts

f. Trientine (triethylenetetramine HCl) is a polydentate chelating agent. It chelates copper and less toxic than penicillamine, but it is teratogenic in long term use. It is used for treating wilson's disease (hepatolenticular degeneration).

A. Structure



4. CONCLUSION

Heavy metals are individual metals and metal compounds that can impact human health. Eight common heavy metals are discussed in this brief: arsenic, barium, cadmium, chromium, lead, mercury, selenium, and silver. These are all naturally occurring substances which are often present in the environment at low levels. In larger amounts, they can be dangerous.

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