LEARNING TOXICOLOGY THROUGH OPEN EDUCATIONAL RESOURCES

Copper

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COPPER *(Lat. Cuprum, Cu)*

a metal widely distributed in nature

Cu is an essential micronutrient, but it is toxic in excess.

Copper toxicity is also called copperiedus

Cu has been used for many centuries. In Roman times, copper became known as cyprium, because it was mined in Cyprus.

1. Sources and uses:

Industry:

- ✓ smelting and welding operations
- ✓ manufacturing corrosion resistant plumbing pipes, cookware
- ✓ component of alloys (with white gold or zinc) used in dental products, jewelry, coins
  brass (metal alloy made of Cu + Zn), bronze (Cu + Sn)

Agriculture:

- ✓ salts are used as fungicides and insecticides (e.g. treating grape vines)

Medicine:

- ✓ Cu spermatocide intrauterine devices
- ✓ Supplements
- ✓ Copper sulfate ($CuSO_4$) because of its toxicity is no longer used as an emetic

$CuSO_4$ is sometimes called „blue vitriol“, because it can be prepared by oxidizing Cu in hot concentrated H_2SO_4 („oil of vitriol“).

2. Functions in the organism:

Cu is essential for many biological processes:
Cu is a component of many oxidative enzymes, including cytochrome oxidase, monoamine oxidase, catalase, peroxidase, zinc / copper superoxide dismutase
Cu is required for the formation of myelin (a protective layer covering neurons) and it is involved in formation of melanin (pigment in hair, eyes and skin).
Cu is essential for the utilization of iron. Iron-deficiency anemia in infancy is sometimes accompanied by cooper deficiency as well.

Cu deficiency is associated with hypochromic, microcytic anemia resulting from defective hemoglobin synthesis (refractory to Fe supplementation), leukopenia and pathologic effects on the cardiovascular, skeletal and nervous system.

Recommended daily intakes of Cu varies according to age, pregnancy…
It is about 2 mg for adult

Cu deficiency is uncommon in humans. It can occur as a result of malnutrition or excessive consumption of zinc. Drinking water contributes about 6-13% of the average daily intake of Cu.

3. Fate in the organism:

Cu homeostasis is regulated through a complex system of Cu transportes and chaperone proteins.

Absorption:

Copper salts are primarily absorbed in the duodenum. Dietary Cu is absorbed after reduction into cuprous ions (Cu^{1+}). Intestinal absorption is normally regulated by body stores and can be reduced by Zn, Fe, fructose.

Distribution:

In plasma, Cu is transported in the oxidized cupric form (Cu^{2+}) bond to albumin and ceruloplasmin. Most cooper is stored in liver and bone marrow, where it may be bound to metallothionein.

Excretion:

The bile is the normal excretory pathway and plays the primary role in cooper homeostasis. Within 3 days, 1% of Cu is excreted in the urine and 10% in the feces.

The amount of cooper in milk is not enough to maintain adequate cooper levels in the liver, lung and spleen of the newborn.

Cu is generally well-tolerated:

Safe doses are up to 5 mg/day in healthy adult.

Doses of ≥ 7 mg/day may produce nausea, vomiting, diarrhea

Higher doses can cause liver damage.

There are two genetically inherited inborn diseases of copper metabolism:

a) *Wilson´s disease* (hepatolenticular degeneration)

= autosomal recessive genetic disorder

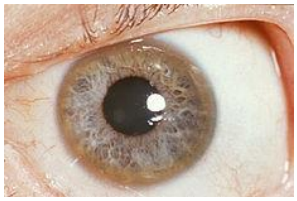
The cause of this disease is defective gene (ATPB7) in chromosome 13, which codes Cu transporting protein (ATP-ase responsible for excretion of Cu to the bile). Result of impaired biliary excretion of Cu and low Cu binding to ceruloplasmin is excessive accumulation of copper in liver, brain, kidneys and cornea. Clinical abnormalities of the nervous system, liver, cornea and kidney are related to copper accumulation.

Hepatolenticular degeneration = disease with hepatic symptoms and neurological symptoms (results from damage of the lenticular nucleus of basal ganglia).

For more see:
https://neurowiki2012.wikispaces.com/Wilson%E2%80%99s+Disease

Clinical improvement can be achieved by chelatation of copper. However, drugs must be taken life-long.

Wilson's disease has been known since the early 1900s, when two doctors described rings in corneal pigmentation (the Kayser–Fleischer ring).



b) Menke´s disease

= a rare sex-linked genetic defect in Cu metabolism resulting in Cu deficiency in male infants.

It is characterized by peculiar hair, severe mental retardation, neurologic impairment and death before 5 years of age. There is extensive degeneration of the cerebral cortex and of white matter.

The basic defect is in copper transporter. Deficiency in this transporter blocs Cu transport across the basolateral membrane of intestinal cells into the portal circulation, resulting in accumulation of Cu in the enterocytes and the systemic deficiency in the body. The transport of Cu to the brain is also blocked, causing severe neurological abnormalities.

Share video: https://www.youtube.com/watch?v=yWJ8lpR2fcU

https://www.youtube.com/watch?v=k44aaLsxxw8

4. Intoxication:

A tight control of Cu homeostasis prevents excess accumulation of Cu in the body, acute and chronic Cu toxicity are relatively rare. However, Cu toxicity may result from exposure to excess Cu caused by accident, occupational hazard, environmental contamination or inborn errors of Cu metabolism.

Acute poisoning.

Results usually **from ingestion of excessive amount of oral copper salts**, most frequently copper sulfate. $CuSO_4$ is highly irritating, may produce mucous membrane irritation and nausea, blue-green emesis and severe gastroenteritis with hepatic failure. GIT bleeding may occur. Fluid and blood loss from gastroenteritis may led to hypotension and oliguria. Individuals with glucose-6-phosphate deficiency may be at increased risk of the hematologic effect (hemolytic anemia) of copper. Intravascular hemolysis can result in acute tubular necrosis. Multisystem failure, shock and death may occur.

Ingestion of 10 to 20g of $CuSO_4$ is usually lethal

Elemental Cu is poorly absorbed orally and practically non-toxic.
However, **inhalation of Cu dust, or metal fumes** may cause chemical pneumonitis or syndrome similar to metal fume fever.
In the eye metal Cu dust may lead to corneal opacification, uveitis and even blindness unless the dust is removed quickly.

Churches in some developing countries distribute „spiritual green water“ containing Cu salts. After ingestion, serious toxicity and even death can result.

Chronic poisoning.

Chronic exposure is usually associated with development of hepatic injury and cirrhosis.

Occupationally: inhalation of Bordeaux mixture ($CuSO_4$ with hydrated lime) in vineyars workers may result in lung damage (fibrosis, lung cancer) and liver damage (fibrosis, cirrhosis).

Excessive dietary Cu intake → **Indian childhood cirrhosis:**

= disease observed in children in India after drinking milk boiled and stored in copper or brass pots. This disorder is characterized mainly by jaundice and liver injury (cirrhosis).

Also in other countries (e.g. in Austria in Tyrol region), where people use copper vessels to store milk, children suffer from similar symptoms (= **non-Indian childhood cirrhosis or idiopathic copper toxicosis)**

Children have probably increased susceptibility to copper toxicity because homeostatic mechanisms are not fully developed at birth.

There are currently no indications of mutagenic or carcinogenic effects of copper.

5. Mechanism of toxicity:

There are many mechanisms involved, e.g. free Cu levels potentiate the formation of ROS and result in oxidative stress.

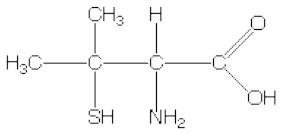
6. Laboratory determination:

Cu poisoning diagnosis is based on an elevated serum level.
Normal serum concentration average is 1 mg/L. Serum Cu levels above 5 mg/L are considered very toxic.

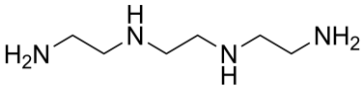
7. Treatment:

Copper deficiency is treated by administration of Cu compounds (copper orotate or gluconate) and/or food rich in Cu (e.g. cacao and its products, mushrooms).
As copper chelators, the following are currently used:

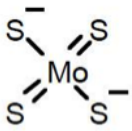
D-penicillamine - is used the most widely for the treatment of Wilson disease. It has severe adverse effects (concerning kidney, immune system, connective tissue) and it can worsen central symptoms of Wilson disease.



Triethylene tetramine dihydrochloride (*trientine,* trien, TETA) – is effective drug with less side-effects.



Tetrathiomolybdate (TTM) – suitable for patients who are intolerant to D-penicillamine and trientine.



Zinc salts limit Cu-absorption in the intestine. Zn stimulates metallothionein synthesis in the enterocytes, which have then a higher capacity to chelate dietary Cu and therefore limit Cu-transfer into the portal circulation. However, this medication is mainly used to treat asymptomatic patients or for maintanance.

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