Heavy metals toxicity

HEAVY METALS

- IRON √
- LEAD √
- MERCURY
- ARSENIC
- NICKEL

- CADMIUM
- THALLIUM
- ALUMINUM
- GOLD

- Some metals needed in trace amounts
- Body lacks any major system to remove excess metals

HEAVY METALS

IRON TOXICITY

IRON

- **CHRONIC IRON TOXICITY?**
- Hereditary hemochromatosis due to abnormal absorption of iron from the intestinal tract
- Excess intake via the diet or from oral iron preparations
- Repeated blood transfusion for some forms of anemia

IRON

- Accidental ingestion of iron containing preparation is relatively common among children…3g lethal in 2yrs old
- Available as iron supplement tablets, multiple vitamin-mineral products
- May be found as gluconate, sulfate and fumarate

Salt	Elemental iron %
Ferrous sulfate	20
Ferrous gluconate	11.6
Ferrous fumarate	33

IRON

- Toxicity related to the actual amount of elemental iron in the product

  EXAMPLE:

  a 325 mg tablets of ferrous sulfate contains 65 mg of elemental iron

- **< 20 mg/kg considered nontoxic**
- **20-30 mg/kg potentially toxic (self-limited vomiting, abdominal pain, & diarrhea)**
- **> 40 mg/kg Potentially serious**
- **> 60 mg/kg Potentially lethal**
- **> 150 - 200 mg/kg lethal**

IRON

- 2 types of body iron
  - **Heme iron**
    - Hemoglobin, myoglobin, catalases, peroxidases, cytochromes (a, b and c – involved in electron transport), cytochrome P450 (involved in drug metabolism)
  - **Non-heme iron**
    - **Ferritin**, **hemosiderin**, **transferrin**, ferroflavoproteins, aromatic amino acid hydroxylases
- Food iron is also classified as heme and non-heme

Food iron

Heme iron

- meats
- poultry
- fish

Non-heme iron

- vegetables
- fruits
- legumes
- nuts
- breads and cereals

20-23% of heme-iron is absorbable

only ~ 3% on non heme iron is absorbed

IRON

- The **4th most abundant element in the earth crust**
- **Most abundant trace element in body**
- **Needed in trace amounts**
- Total dietary intake 10 - 15 mg daily, only 10% absorbed
- It occurs in two forms…**ferrous or ferric**

IRON ABSORPTION

- **Ferrous** is **better absorbed** than **ferric** form
- Occurs in upper part of small intestine
- Requires gastric HCl (maintains iron in a soluble state)

IRON DISTRIBUTION AND STORAGE

- Iron is **oxidized to its ferric state** and couples to **transferrin**....carried in **blood stream** (glycoprotein)
- **80-90% of abs. iron** is transferred to **bone marrow…erythropoiesis**
- **Excessive iron is stored** in the body as 2 forms:
  - **Ferritin** (a **water soluble** complex consisting of a core of ferric hydroxide and a protein shell (apoferritin)
  - **Hemosiderin** (a **particulate substance** consisting of **aggregates** of ferric core **crystals**)

IRON

- Stored in **liver**, **spleen**, **bone marrow**, **intestinal mucosal** cells and **plasma**
- Trace amounts are lost in **bile**, **urine** and **sweat** (no more than 1 mg per day)
- **There is no mechanism for excretion of iron**
- Iron is **normally lost by exfoliation of intestinal mucosal cells into the stools**

Epidemiology

- In 2015, the Annual Report of the American Association of Poison Control Centers (AAPCC) National Poison Data System reported 4072 single exposures to iron or iron salts. Out of these, 3211 cases were unintentional ingestion. Furthermore, 2036 of reported cases occurred in children 5 years old or younger, and 1161 cases were treated in a healthcare facility. There was one death.

IRON TOXICITY

- Normal serum iron is 50 - 150 ug / dl
- Does this mean that doubling intake will initiate toxicity?
- Serum iron below **300 ug / dl** usually non toxic
- Normal transferrin 1/3 saturated
- About 20-50% of the iron-binding sites are filled
- Toxicity when the serum iron > TIBC….free iron is present in the serum

❖ (TIBC = total iron binding capacity)

Mechanism of toxicity

- Toxicity results from **direct corrosive effects** and **cellular toxicity**:

A. Iron has a direct corrosive effect on mucosal tissue (GI) and may cause **hemorrhagic necrosis** and **perforation**

B. The presence of free iron in the circulation directly affect the **metabolism**, the **GIT**, **liver**, **CVS** and **CNS's**

- Iron enters the mitochondria and acts as a **catalyst** of **lipid peroxidation** resulting in **cell damage**….oxidative degradation of lipid by free radicals

Toxicity

- **GIT**: direct corrosive action on mucosal surface…hemorrhagic necrosis, perforation and infarction of the distal small bowel
- **CVS**: plasma volume drops, bleeding, hypotension, tachycardia and compensatory vasoconstriction …..cardiogenic shock
- **Hepatic effects**: range from swelling to necrosis of hepatocytes
- **Metabolic effects**: generation of profound metabolic acidosis….(mitochondrial dysfunction forcing anaerobic resp.)
- **CNS**: range from **depression to coma** (acidosis & poor perfusion)

IRON

CLINICAL PRESENTATION:

- **Stage 1: within 6hrs; abdominal pain, N,V, D, bloody diarrhea…direct corrosive effect on intestinal mucosa**
- **N.B:** massive **fluid or blood loss** may result in **shock**, **renal failure**, and **death**
- **Stage 2:** victims who survive this phase may experience a **latent period** of **apparent improvement** over **12 hours**…..quiescent phase….**falsely stable**….
- **Stage 3: 12 to 48 hrs worsening of GI hemorrhage, coma, shock, seizures, metabolic acidosis, coagulopathy, hepatic failure**, and **death**

IRON

CLINICAL PRESENTATION:

If the victim survives:

- **Stage 4:** **2 - 4 days** post ingestion, **hepatic failure, elevated transaminase enzymes**
- **Stage 5:** **2 - 4 weeks, GI obstruction, cirrhosis**

Diagnosis

- Based on a history of exposure and the presence of **nausea, vomiting, diarrhea, & hypotension**
- **Specific levels.** If the total **serum iron level is higher than 450–500 mcg/dL**, toxicity is more likely to be present
- Serum levels higher than **800–1000 mcg/dL are associated with severe poisoning**
- **Determine** the serum iron **level** at **4–6 hours after ingestion** and **repeat determinations after 8–12 hours to rule out delayed absorption** (eg, from a sustained-release tablet)
- **Other useful laboratory studies** include CBC, electrolytes, glucose, BUN, creatinine, hepatic aminotransferases (AST and ALT), coagulation studies, and abdominal radiography

MANAGEMENT

1. *GENERAL*

- **ABC's**

- **Gastric lavage** with normal saline

✓ Not **bicarbonate** (hypernatremia, alkalosis) and **phosphate solutions (hypernatremia, hyperphosphatemia, hypocalcemia)**

✓ Not **deferoxamine solution** (may enhance iron absorption)

- Subsequent **radiographs** of abdomen to look forward remnant pills

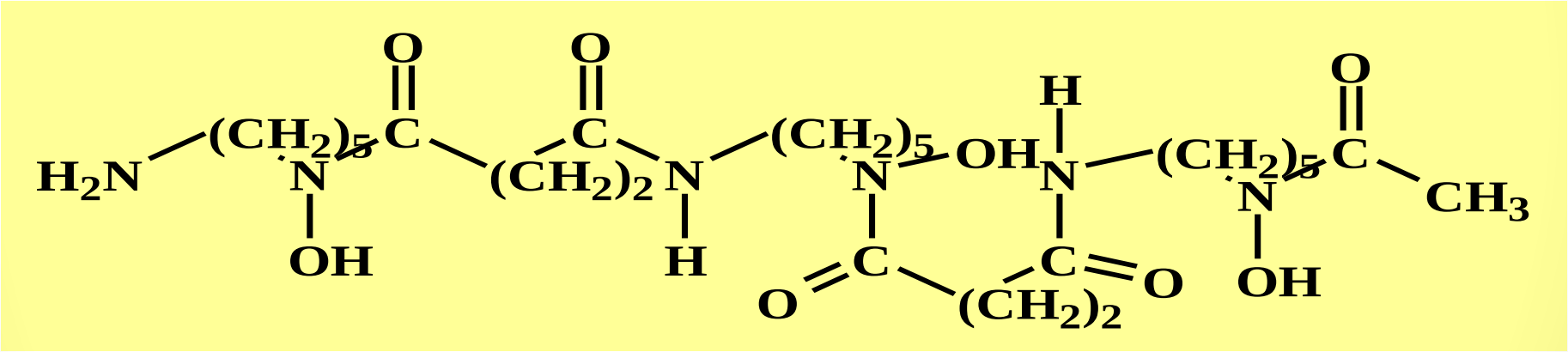
MANAGEMENT

1. ***GENERAL***

- **Whole bowel irrigation** (iron tab beyond the pylorus)
- **Activated charcoal** does not adsorbed Fe
- **Ipecac** is not recommended because it can aggravate iron-induced GI irritation
- **Cathartics** usually not necessary

2. TOXIN SPECIFIC MEASUREMENTS

- Deferoxamine



Deferoxamine mesylate (DFOM)

CHELATION: DEFEROXAMINE

- For seriously intoxicated victims (eg, shock, severe acidosis, and/or serum iron >500–600 mcg/dL), administer **deferoxamine**

❖ **Specific chelator of ferric ion** which reacts with ferric ion to form a 1:1 chelate known as **ferroxamine**

- It **binds free circulating iron** but not that incorporated in transferrin, hemoglobin….

  ❖ Limit the entry of iron in the cells

  ❖ Chelate intracellular free iron outside mitochondria

CHELATION: DEFEROXAMINE

- Poorly absorbed from GIT…**given <u>parenterally (IV/IM)</u>**
- However the iron-deferoxamine complex is absorbable
- Use in symptomatic patients, Fe > 500 ug/dl, or positive radiographs
  - ✓ 100 mg chelates 9 µg of Fe
  - ✓ Constant I.V infusion 10-15 mg/kg/hr for 24h (max daily dose of 6g)
  - ✓ Dose I.M = 50 mg / kg (max 1g)
  - ✓ <u>*Vin – rose-colored* urine…excretion of complex</u>

DEFEROXAMINE SIDE EFFECTS

1. **HYPOTENSION** (histamine-mediated vasodilation)

   Usually respond to iv fluids

2. **EXCRETION OF FERROXAMINE is by kidney**…

   In renal failure, hemodialysis is indicated to remove complex

3. **PREGNANCY**

   Pregnancy should not change the management of iron poisoning

Enhanced Elimination

- **Hemodialysis and hemoperfusion** are **not effective** at removing iron but may be necessary to remove deferoxamine-iron complex in patients with renal failure

- **Exchange transfusion** is used occasionally for massive pediatric ingestion but is of questionable efficacy