Artery Academy

Alaa malkawi

Heavy metals toxicity

HEAVY METALS

- IRON √
- LEAD √

روح ذهبي عن صدك

- MERCURY
- ARSENIC
- NICKEL
- CADMIUM
- THALLIUM
- ALUMINUM
- GOLD

* iron is imp for heme. Formation ←

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

Metal are removed by

renal excretion

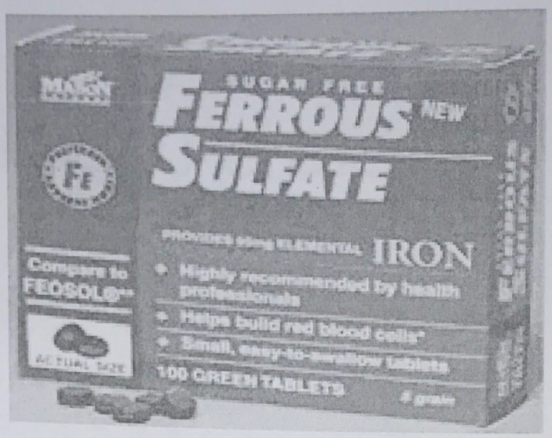
pulmonary excretion

* plays arole in som enzymatic reactions for energy production

ماني طوق تانية عشان صير chance يصير for Metals Toxicity

HEAVY METALS

IRON TOXICITY



acute iron Toxicity happens → يتصير بحالة ال over dose من iron

IRON

- **CHRONIC IRON TOXICITY?**

genatic cause

- Hereditary hemochromatosis due to abnormal absorption of iron from the intestinal tract

* deficte in certain gens (HFE genc) wich increases The absorption of iron

- Excess intake via the diet or from oral iron preparations

* iron ال يوصل absorption ال steady state من اكثر

- Repeated blood transfusion for some forms of anemia

and There is no extra absorption
يس بعض الناس يصير او يكون عندهم خلل بهاد الجين فيصير عندهم increase in iron absorption

Times → which Leads iron accumilation in The body → Leads to organs damage

IRON

بحالة الـ acute

- 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 ① gluconate, ② sulfate and ③ fumarate

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

الكتر واحد الله chance للـ Toxicity بسبب انه الـ iron اعلى

بهمنا كل salt ← كم بيحتوي Elemental iron

IRON

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

EXAMPLE:

Stages of Toxicity and symptoms are dose dependent

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) → GI A.R
- > 40 mg/kg Potentially serious
- > 60 mg/kg Potentially lethal
- > 150 - 200 mg/kg lethal → القاتلة

IRON

- 2 types of body iron

1. Heme iron

e.g:
- Hemoglobin, myoglobin, catalases, peroxidases, cytochromes (a, b and c – involved in electron transport), cytochrome P450 (involved in drug metabolism)

enzyme (antioxidante enzyme)

2. Non-heme iron

iron Forms in the body
- **Ferritin**, **hemosiderin**, **transferrin**, ferroflavoproteins, aromatic amino acid hydroxylases

- Food iron is also classified as heme and non-heme

Food iron

Heme iron → easly absorbed

- meats
- poultry
- fish

Non-heme iron

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

* we can get it from animal sources *
* easly absorbed *

20-23% of heme-iron is absorbable

only ~ 3% on non heme iron is absorbed

* بنعزز الـabsorbtion بـ Heme iron
↳ by using vitamin C

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
  ↳ dietary intake لو كان الـ non-heme هي اللي absorbed فإن بكون اقل من 10%
- It occurs in two forms...ferrous or ferric
  1. ferrous → Fe^{+2} → better absorbed
  2. ferric → Fe^{+3}

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)

↳ Ferric لتحويل ال
↳ Ferrous → For Better absorption
خاصة بـ non-heme iron

IRON DISTRIBUTION AND STORAGE

iron → Transferrin بيربط
Transport حتى يصيره

- Iron is **oxidized to its ferric state** and couples to **transferrin**....carried in **blood stream** (glycoprotein)
  ← الناقل اللي بينقل الـ iron من الـ duodenum → To the bone marrow (storge place)
- **80-90% of abs. iron** is transferred to **bone marrow...erythropoiesis**
  يصيره storge
- **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))
    ← بيتخزن على شكل
  - **Hemosiderin** (a **particulate substance** consisting of **aggregates** of ferric core **crystals**)

IRON

Main storge Site

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

Epidemiology

الارقام موحفظ

- 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 Toxicty → اكتر شي بيصير عند الـ Childrens

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

* ممكن تركز على الي عليه هايلايت بس معلومات

- **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.)
  السبب ← Mitochonderia accumli of iron → which leads to free redical genieration
- **CNS:** range from **depression to coma** (acidosis & poor perfusion)

IRON

كل ما تأخرنا بتزيد الـ stage

CLINICAL PRESENTATION:

- Stage 1: **within 6hrs; abdominal pain, N,V, D, bloody diarrhea**...direct corrosive effect on intestinal mucosa → GI A.E
- N.B: massive **fluid or blood loss** may result in **shock, renal failure, and death**
  يتصل
  بسبب exissive of blood loss
- Stage 2: victims who survive this phase may experience a **latent period** of **apparent improvement** over **12 hours**.....quiescent phase....falsely stable....→ يعني ممكن يبين وضعه مستقر فجأة بينتقل المريض لـ stage 3 ← عشان هيك لازم يضل للمريض تحت الرعاية
- 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: * اذا ما مات من stage 3 بدخل لل stage 4 الاصعب

- **Stage 4: 2 - 4 days** post ingestion, **hepatic failure, elevated transaminase enzymes**

Latent stage

- **Stage 5: 2 - 4 weeks, GI obstruction, cirrhosis**

Diagnosis

patient condition / route of exposure / History of exposure يعتمد على ال age / signs and symptoms

- 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)

in stage one يجبين لها بدخل ب stage 2 يعني بين 8 - 12 hr للازم اعيد Test ال

- **Other useful laboratory studies** include CBC, electrolytes, glucose, BUN, creatinine, hepatic aminotransferases (AST and ALT), coagulation studies, and abdominal radiography → To rule out liver adverse reactions

↳ if there's bleeding

لكونه ممكن اعتمد انه ال iron conc قاعد بنزل و يكون بالعكس بزيد → الـ Toxicity لتكون ليتصير من ال Sustained release Tablets

MANAGEMENT

1. GENERAL

- **ABC's**

* AC ما بستخدم لأنه iron is poorly absorbed with AC

- **Gastric lavage** with normal saline

Fluids in gastric Lavage بحتاجهم اذا كان عندي Small Tablets او Chewable Tablets او Liquid solut لأنه حكينا Large tablets cannot bass through The Tube of gastric Lavage

✓ 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

* defroxamine → given IV not by gastric Lavage

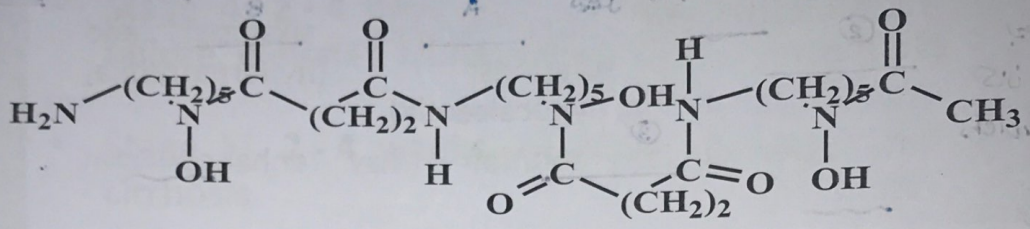
MANAGEMENT

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 → Antidote in iron poisining
  * Chelating agent



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.... → برتبط

  ❖ Limit the entry of iron in the cells

  ❖ Chelate intracellular free iron outside mitochondria

بار Free iron

هو بار Hemo او Transferrin

CHELATION: DEFEROXAMINE

- Poorly absorbed from GIT...**given parenterally (IV/IM)**
- 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)
  - ✓ *Vin – rose-colored* urine...excretion of complex

infusion not bulse لازم
IV Bolse ال ممكن يعمل Anaphlactic reactions

it can induce Histamine release which leads to vasodilation الي بعمل Hypotension

بنوفق ← Therapy ال لما يتحول لون ال urine To the normal Color

This Means iron in the serum started to decrease

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

اذا كان في RF → ما بنعطي defroxamine لانه بصير accumilation complex لهاد ورح يصير له او نغله removing By Hemodialysis

Toxicity

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