

# Heavy metals toxicity

"اللهم افتح عليّ أبواب رحمتك، ويسّر لي فهم ما أدرُس، وامنحني قوة الحفظ وصفاء الذهن، واجعل التوفيق حليفي في كل خطوة."

by Noor Mansour

"شابتّر خفيف لحليف"

# HEAVY METALS

بمنتهائهم الجسمنا بس اذا زادت البرعة رح نوصن  
لا toxicity

- IRON ✓
- LEAD ✓
- MERCURY
- ARSENIC
- NICKEL
- CADMIUM
- THALLIUM
- ALUMINUM
- GOLD

اكثر 2 رح  
نركز عليهم لانهم  
common

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

عن طريق البوليary excretion or renal excretion (طاعنا طرقت ثانية او  
مثلا" انذيجات او specific system عشان يعمل remove لهي Metals)

# HEAVY METALS

iron supplement

IRON TOXICITY



# IRON

- acute: exposure to an even dose of iron
- chronic: hemochromatosis

- **CHRONIC IRON TOXICITY?**

- (defect in certain) وراثي (defect in certain gene) Hereditary hemochromatosis due to abnormal absorption of iron from the intestinal tract  
↑ because of iron overload  
→ acute بالحاد
- ② Excess intake via the diet or from oral iron preparations  
→ Hereditary & acquired cause
- ③ Repeated blood transfusion for some forms of anemia or thalassemia

# IRON

acute (unintentional)  
غير مقصود

- Accidental ingestion of iron containing preparation is relatively common among children... 3g lethal in 2yrs old

LD for children in 2yrs old

- Available as iron supplement tablets, multiple vitamin-mineral products

- May be found as gluconate, sulfate and fumarate

11.6%

20%

الأشكال الموجودة فيها Iron

33%

| Salt                                        | Elemental iron % |
|---------------------------------------------|------------------|
| Ferrous sulfate                             | 20               |
| Ferrous gluconate                           | 11.6             |
| Ferrous fumarate → الأكثر ودية<br>فيها حديد | 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%.

$$\begin{array}{rcl} x & \longrightarrow & 325 \\ 20 & \longrightarrow & 100 \end{array}$$

- **< 20 mg/kg considered nontoxic**  $x = 65$
- **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** جرعة قاتلة.

# IRON

- 2 types of body iron

أنشكال Iron في الجسم:

- **Heme iron**

في الصفات  
↑

1- Heme  
2- Non-heme

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

- **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

حتى بالهده في  
Heme and Non-heme

From animal  
↑ source

# Food iron (in diet)

## Heme iron → easily absorbed

- meats
- poultry
- fish

## Non-heme iron

- vegetables
- fruits
- legumes (البقوليات) (عدس)
- nuts
- breads and cereals

20-23% of heme-iron is absorbable

only ~ 3% on non heme iron is absorbed

\* عسلان هيل بنوفه فيتامين C مع الحديد عسلان يحسن الامتصاص.

# IRON

الموجودة على الأرض

- The 4<sup>th</sup> most abundant element in the earth crust

← هاي الجمل  
هي في  
الامتحان

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



↓  
امتصاص احسن

# IRON ABSORPTION



- **Ferrous** is better absorbed than ferric form

- Occurs in upper part of small intestine ↪ absorption موقع

why? ↪

- 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)

الناقل تبع iron

- 80-90% of abs. iron** is transferred to **bone marrow...erythropoiesis**

80-90% يذهبوا للbone وliver. erythropoiesis و يكون hemoglobin حشان يكون RBCs

- Excessive iron is stored** in the body as 2 forms:

- ① **Ferritin** (a **water soluble** complex consisting of a core of **ferric hydroxide** and a protein shell (apoferritin))

الحديد الزيادة يكون على شكل ① + ②

- ② **Hemosiderin** (a **particulate substance** consisting of **aggregates** of ferric core **crystals**)

# IRON

→ for RBCs production

- 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**  
shedding
- Iron is normally lost by **exfoliation** of **intestinal mucosal cells** into the **stools**

فقدان الحديد  
من  
سائل

# Epidemiology

علم الوبئة

\* الأرقام متشعبة للحفظ \*

- 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 <sup>غير مقصود</sup>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.

\* أكثر حالات iron toxicity في الأطفال

هائي الإشارة (✱) معناهم مهم

# 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 → Free iron لا يسمح للaccumulation في serum بل سببه toxicity
- ❖ (TIBC = total iron binding capacity)

— عندى ناقل ينقل Iron من intestine لا storage sites اذى عندى high amount of absorption يعنى اعتر من (TIBC) لا يسمح بـ accumulation في serum وانما كانت اكثر من 300 ug/dl تكون toxic.

# Mechanism of toxicity

- Toxicity results from **direct corrosive effects** and **cellular toxicity**: → dose dependent & stage dependent
- A. Iron has a direct corrosive effect on mucosal tissue (GI) and may cause **hemorrhagic necrosis** and **perforation**  
↳ GI bleeding
- B. The presence of free iron in the circulation directly affect the **metabolism**, the **GIT, liver, CVS** and **CNS's**  
↳ enhance energy production
- Iron enters the mitochondria and acts as a catalyst of lipid peroxidation resulting in **cell damage**....oxidative degradation of lipid by free radicals  
↳ tissue damaged & cell injury

\* رعوذا عالحكفوبه باهه \*

# 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 and hepatic injury
- **Metabolic effects:** generation of profound metabolic acidosis....(mitochondrial dysfunction forcing anaerobic resp.)  
Free radical generation
- **CNS:** range from depression to coma (acidosis & poor perfusion)

# IRON

## CLINICAL PRESENTATION:

→ GI symptoms

Neusee ↑ Vomiting ↑ → Diarrhea

- **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 → اذا ما تبالغ بسرعة  
→ 6-12 hrs
- **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 (ALT, AST)  
↳ bilirubin
- Stage 5: 2 - 4 weeks, GI obstruction, cirrhosis

# Diagnosis

Depend on

- 1- History
- 2- Route of exposure
- 3- patient condition
- 4- Age
- 5- 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)   
 *Stage one*  
 *Repeat determin - iron concentration* *لأنه ممكن يزداد*
- **Other useful laboratory studies** include **CBC, electrolytes, glucose, BUN, creatinine, hepatic aminotransferases (AST and ALT), coagulation studies, and abdominal radiography**

*اذا عثري bleeding (عن هزيت) (NR)*

# MANAGEMENT

## 1. GENERAL

### • ABC's

→ circulation  
← Breathing  
Airway ←  
فسيحة صدرية

- Gastric lavage with normal saline → liquid on ← iron is on  
small size لا tablet

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

✓ Not deferoxamine solution (may enhance iron absorption)

يزيد الامتصاص الحديدي

- Subsequent radiographs of abdomen to look forward remnant pills

activated charcoal لا يمتص الحديد  
poorly absorbed لا iron

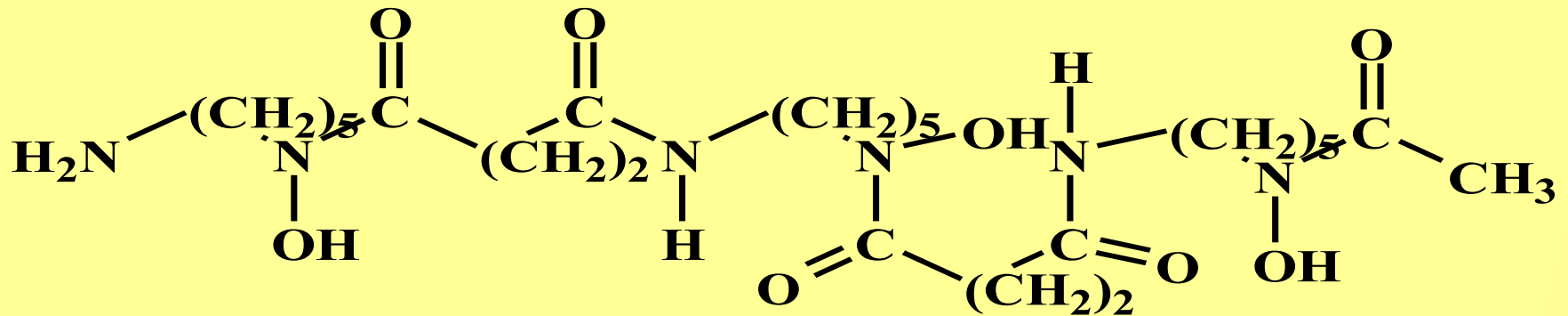
# MANAGEMENT

## 1. **GENERAL**

- **Whole bowel irrigation** (iron tab beyond the pylorus)
- ~~\*~~ **Activated charcoal** does not adsorb Fe  
    → GI irritation & de.
- ~~\*~~ **Ipecac** is not recommended because it can aggravate iron-induced GI irritation
- ~~\*~~ **Cathartics** usually not necessary

## 2. TOXIN SPECIFIC MEASUREMENTS

- Deferoxamine → antidote  
↓  
chelating agent



Deferoxamine mesylate (DFOM)

# CHELATION: DEFEROXAMINE

↳ For serious intoxication

- 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 complex  
وینعطر ۱۷
- It **binds free circulating iron** but not that incorporated in transferrin, hemoglobin... → ما برتبه فیهم  
برتبه بس بال free
- ❖ Limit the entry of iron in the cells
- ❖ Chelate intracellular free iron outside mitochondria

ما يتعلق  
of all y ↑

# CHELATION: DEFEROXAMINE

- Poorly absorbed from GIT...given parenterally (IV/IM)
- However the iron-deferoxamine complex is absorbable
- Use in symptomatic patients,  $Fe > 500 \text{ ug/dl}$ , or positive radiographs
  - ✓ ~~100 mg chelates  $9 \mu\text{g}$  of Fe~~
  - ✓ ~~Constant I.V infusion 10-15 mg/kg/hr for 24h~~  
(~~max daily dose of 6g~~) → not bolus
  - ✓ ~~Dose I.M = 50 mg / kg (max 1g)~~
  - ✓\* Vin – rose-colored urine...excretion of complex

↓  
urine لونه وردية يعني فيه Iron secretion  
وإذا رجع لونه طبيعي بوقف العلاج لأن Iron فيه  
serum قل.

# DEFEROXAMINE SIDE EFFECTS

## 1. HYPOTENSION (histamine-mediated vasodilation)

Usually respond to iv fluids (infusion not bolus)

## 2. EXCRETION OF FERROXAMINE is by kidney...

In renal failure, hemodialysis is indicated to  
remove complex

لا ينجح Ferroxamine في حالة  
renal failure حيث أن  
accumulation  
لا ينجح Complex، وذلك في حالة  
hemodialysis.  
لأن Complex لا ينجح في إزالة.

## 3. PREGNANCY

Pregnancy should not change the management of iron  
poisoning

# Enhanced Elimination

deferoxamine ممكن نستخدمه مع الناس الي اقدت  
وهي رعا Renal failure

- **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

ممكن متاعدين  
من خفالية

نقل الدم

للاطفال