L4-HEAVY METALS

هذه المذكرة شاملة كل
محتوى سلايدات الدكتور!

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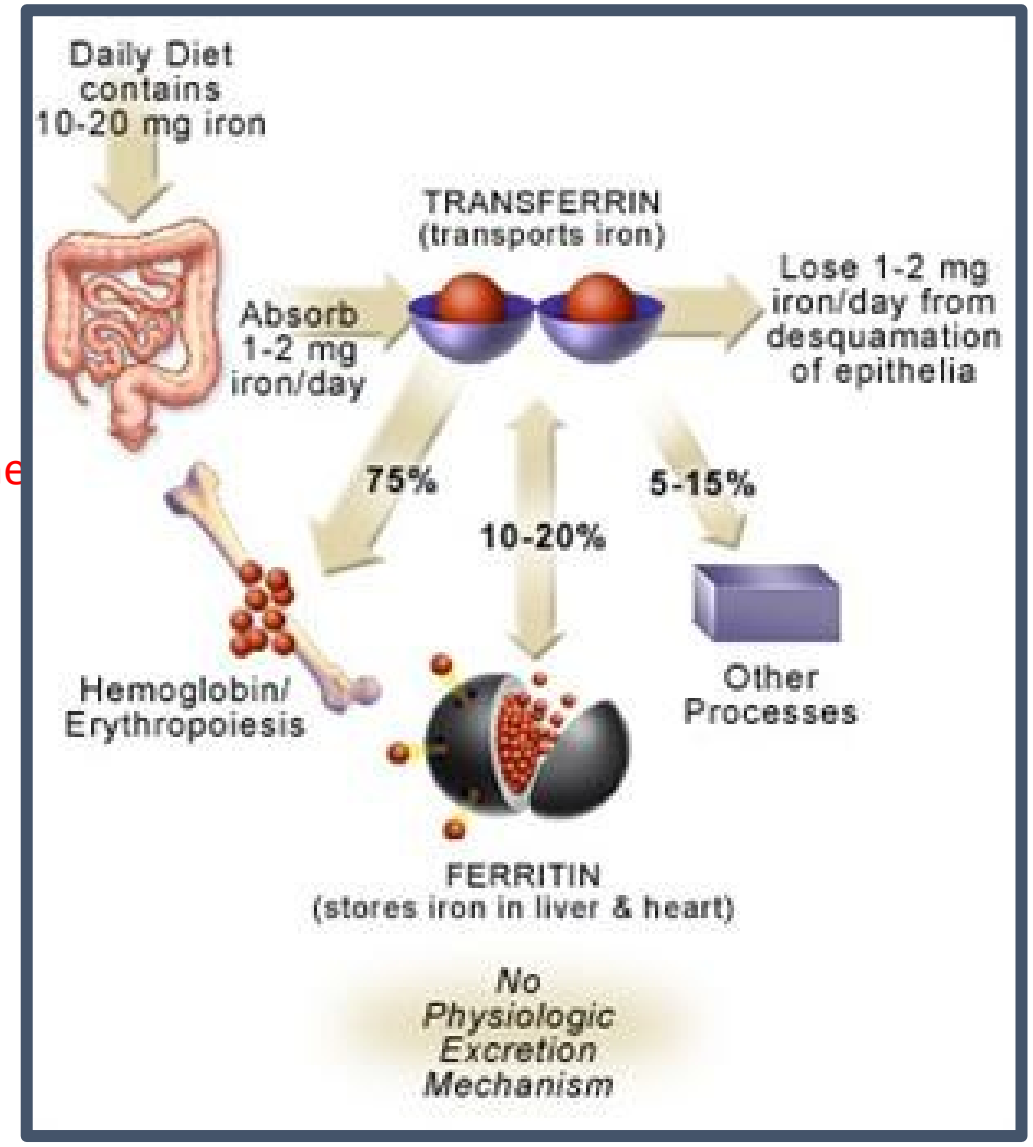
Objectives:

Red: important

Editing File

Iron (Fe)

- Highly toxic to the children younger than age 6
- Adult : suicide attempts.
- Normal serum iron levels : 50 to 150 micg/dL. Similar to creatinine level
- The total iron-binding capacity (TIBC), a crude measure of the ability of serum proteins—including transferrin—to bind iron, ranges from 300 to 400 micg/dL.
- When iron levels rise following a significant iron overdose, transferrin becomes saturated so that excess iron circulates as free(unbound) iron in the serum wich is toxic.
- >20 mg/kg:observed without further therapy. no symptoms.
- 20 to 60 mg/kg mild to moderate symptoms.
- ingestion of more than 60 mg/kg may lead to severe morbidity
- 50% mortality (LD_{50}) is reported to be 200 to 250 mg/kg.



Pathophysiology

- Two distinct toxic effects:
- (1) it causes injury to the gastrointestinal mucosa
- (2) it impairs cellular metabolism, primarily of the heart, liver, and central nervous system (CNS).
- Unbound (free) iron moves into cells and localizes near the mitochondrial cristae, resulting in uncoupling of oxidative phosphorylation and impairment of adenosine triphosphate synthesis.
- Cell membranes are injured by free radical-mediated lipid peroxidation.
- Iron increases capillary permeability and induces both arteriolar and venodilation.
- Myocardial toxicity decreases cardiac output.
- Hydration of the iron molecule creates an excess of unbuffered protons, worsening metabolic acidosis.
- This multitude of effects, combined with severe gastrointestinal fluid losses, can lead to the development of shock, cardiovascular collapse, and death.

COMPOUND	PERCENTAGE OF ELEMENTAL IRON
Ferrous sulfate	20
Ferrous fumarate	33
Ferrous gluconate	12
Ferric pyrophosphate	30
Ferrocholinate	14
Ferroglycine sulfate	16
Ferrous sulfate, dried	33
Ferrous carbonate, anhydrous	38
Carbonyl iron	100

ELEMENTAL IRON (MG/KG)	PEAK SERUM IRON (µG/DL)	TOXICITY
<20	50–150	None
20–40	150–300	Mild
40–60	300–500	Moderate
>60	>500	Severe

Clinical Features
Five stages. important

- Phase I stomach phase reflects the corrosive effects of iron on the gut. Vomiting occurs within 80 minutes of ingestion in more than 90%of symptomatic cases. Diarrhea, which can be bloody, follows.
- Phase II silent phase represents an apparent (but not complete) recovery that lasts less than 24 hours but can extend up to 2 days. Most patients recover after this point.
- Phase III is characterized by the recurrence of GI symptoms, severe lethargy or coma, anion gap metabolic acidosis, leukocytosis, coagulopathy, renal failure, and cardiovascular collapse.

Serum iron levels may have fallen to normal during this phase due to distribution into the tissues.

Metabolic derangements due to iron poisoning include hypoglycemia, leukocytosis, and severe lactic acidosis from hypoperfusion and interference with cellular respiration.

Early coagulation defects are probably related to direct effects of iron on vitamin K–dependent clotting factors.

Later coagulation : hepatic failure.

- Phase IV, characterized by fulminant hepatic failure, occurs 2 to 5 days after ingestion. This is relatively rare, appears to be dose related, and is usually fatal.
- Phase V represents the consequences of healing the injured gastrointestinal mucosa.

It is characterized by pyloric or proximal bowel scarring, which is sometimes associated with obstruction.

Diagnostic Strategies:

- The presence of gastrointestinal symptoms suggests a potentially serious ingestion, whereas their absence is reassuring.
- A serum iron level: 3 to 5 hours after ingestion, is the most useful laboratory test to evaluate the potential severity of an iron overdose.

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- 350 to 500 micg/dL with moderate toxicity, and greater than 500 micg/dL with potentially severe toxicity.
- iron tablets are Radiopaque on abdominal radiograph.

Management

Gastric Emptying

- Iron is not bound to activated charcoal
- Neither gastric lavage nor ipecac effectively removes large numbers of pills.
- Iron tablets clump together as their outer coatings dissolve.
- Gastrotomy has been
- performed to remove iron
- from the stomach.

• Whole-Bowel Irrigation

- Polyethylene glycol electrolyte lavage solution (PEG-ELS) (CoLyte, NuLytely, or GoLYTELY) is routinely recommended.
- is contraindicated in the presence of bowel obstruction, perforation, or ileus.

- Hemodialysis and hemoperfusion are not effectivein removing iron due to its large volume of distribution.

- Exchange transfusions have been recommended for severely symptomatic patients with serum iron levels exceeding 1000 micg/dL.

- Deferoxamine chelates iron to form the water-soluble compound ferrioxamine,also limit the entrance of iron into the cell
- Pregnancy is not a contraindication to deferoxamine.
- The presence of ferrioxamine turns the urine a “vin ros?” color, which reflects the excretion of chelated iron.

LEAD (Pb)

- Lead poisoning is a disease of industrialization.
- Children typically present to the emergency department :

(1) following an ingestion of lead

(2) symptomatic with a possible exposure history

(3) referred for management of an elevated BLL.

- Lead toxicity in adults most often results from inhalational exposure in the workplace.

- Exposure usually results from ingestion(acute) or inhalation(chronic).
- Found in Lead-based paint ,Curtain weights ,Buckshot ,Fishing weights
- Its absorption is highest in malnourished children (approximately 40%) and in pregnant women.
- Approximately 75% of the absorbed lead is eliminated by the kidneys.

Pathophysiolgy:

- Lead binds to sulfhydryl groups : interferes with critical enzymatic reactions.

Its toxic effects are most prominent in

- Hematopoietic ,Neurologic ,Renal systems.
- It also causes neuropsychiatric disorders
- Anemia : normochromic or hypochromic.
- The severity of the anemia correlates directly with the BLL. Blood Lead Level
- demyelination and degeneration of motor axons result in peripheral neuropathies.
- Lead toxicity also causes neuropsychiatric disorders and hypertension.

- Wrist drop and foot drop are characteristic of adult lead poisoning
- In children, LOW (IQ) scores, hyperactivity, decreased attention span, overaggressive behavior, learning disabilities, criminal behavior, and subclinical sensorineural hearing loss.

- Hyperuricemic gout (“saturnine gout”) can result from increased reuptake of uric acid by the tubular cells.
- Adults and children with acute toxicity may present with lead encephalopathy

clinical feature:

- The diagnosis is suspected by obtaining an accurate and comprehensive history
- Symptoms of chronic, mild lead poisoning are slow in onset and nonspecific, while the Acute exposure to lead can result in symptomatic poisoning.
- “Lead colic” is characterized by cramping abdominal pain with nausea, vomiting, constipation, and, occasionally, diarrhea.
- Fatigue, anemia, peripheral neuropathy, renal impairment, and hepatic and CNS dysfunction.
- The CNS toxicity may manifest as mild headache or personality changes to full-blown encephalopathy with coma, convulsions, and papilledema.
- Permanent neurologic and behavioral sequelae may occur.

Diagnostic Strategies:

- the most informative biomarker is a BLL.
- chronic BLL of greater than 10 micg/dL it is toxic for a child.
- Acute exposure can result in levels up to 100 micg/dL.
- blood cell count, serum glucose, blood urea nitrogen, creatinine, electrolyte levels, and urinalysis.
- A peripheral smear may show basophilic stippling.
- Markers of hepatic injury may be elevated following acute exposure.
- In cases of altered mental status, seizures, or coma, a CT of the head will show cerebral edema associated with acute lead encephalopathy
- In children : (on X-ray)

“lead bands” or “lead lines” that are characteristic of chronic exposures.

Management:

whole-bowel irrigation:

1. Severe poisoning
2. Radiopacities

Activated charcoal does not adsorb lead.

Chelation Therapy:

indicated for Any patient with a BLL greater than 70 micg/dL, or with signs suggestive of encephalopathy.

- Dimercaprol:

✓ forms complexes that undergo both renal and biliary excretion contraindicated in patients allergic to peanuts.

✓ For these seriously poisoned patients, dimercaprol should be the first chelator given.

Adverse reactions to dimercaprol include nausea, vomiting, urticaria, pyrexia, hypertension, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

Dimercaprol is followed by calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$), a highly effective lead chelator.

A BLL of more than 69 micg/dL mandates hospitalization and parenteral chelation therapy.

(2,3-dimercaptosuccinic acid :DMSA)

for Serum lead levels of 45 to 69 micg/dL in patients without vomiting or CNS symptoms can be managed in the outpatient setting.

Oral d-penicillamine should be used only in patients who do not tolerate DMSA.

Penicillin allergy is a contraindication to the use of d-penicillamine.

- No need for chelation for children with a BLL lower than 45 micg/dL.
- If gastrointestinal symptoms or CNS problems are present, hospitalization with parenteral chelation therapy is indicated.
- In the asymptomatic adult or the adult with only mild clinical problems, the only intervention needed is cessation of exposure.
- Patients who have ingested a single lead will usually pass it harmlessly, but If the foreign body remains in the gastrointestinal tract after 2 weeks, removal should be considered to prevent lead toxicity.

ARSENIC (As)

- a tasteless, odorless substance that looks like sugar, has an infamous history as an agent of homicide.
- Inorganic arsenicals are also used in rodenticides, fungicides, insecticides, paint, and tanning agents and as defoliants in the cotton industry.
- Arsenic is still used for medicinal purposes in the treatment of trypanosomiasis, amebiasis, and leukemia.
- found as a contaminant in herbal remedies and drugs such as opium and in Contaminated water.
- trivalent arsenite (As^{3+}) is highly lipid soluble and is 5 to 10 times more toxic than the pentavalent arsenate (As^{5+}) form.
- It is cleared from the intravascular compartment within 24 hours and concentrates in the liver, kidneys, spleen, lungs, and gastrointestinal tract.
- Arsenic crosses the placenta
- Its affinity for sulfhydryl groups in keratin makes arsenic detectable in the hair, skin, and nails.
- **Arsine (AsH_3)** a colorless and almost odorless gas, is extremely toxic, It is immediately lethal at 250 ppm.
- The excretion of arsenic and its metabolites occurs mainly through the kidneys.

- Arsenic binds avidly to sulfhydryl groups, inhibiting critical enzymes such as lactate dehydrogenase and glyceraldehyde-3-phosphate dehydrogenase, a critical step in glycolysis.
- It disrupts oxidative phosphorylation by replacing phosphorus in the formation of phosphate bonds (arsenolysis).
- Arsine causes massive hemolysis.

Clinical Features:

- Acute exposure to arsine gas is characterized by severe hemolysis that is associated with renal tubular injury.
- Gastrointestinal symptoms are common, and CNS and liver dysfunction can occur.
- The mortality rate is 25 to 30%.
- Exchange transfusions and plasma exchange have been used to remove arsine, which is tightly bound to the erythrocytes.
- Urinary alkalinization can be used to decrease renal deposition of hemoglobin
- GIT: nausea, vomiting, abdominal pain, and diarrhea

Initial manifestations of acute exposure to arsenic salts.

- Hematemesis and Hematochezia.
- Within 30 to 60 minutes of exposure, patients complain of a metallic or garlicky taste.

- Encephalopathy with seizures and coma, respiratory failure associated with ARDS and dysrhythmias associated with cardiac conduction disturbances.

- Severe poisoning: cardiovascular collapse and death.
- Less common complications include hepatitis, rhabdomyolysis, hemolytic anemia, renal failure, unilateral facial nerve palsy, pancreatitis, pericarditis, pleuritis ,and fetal demise.

Weeks to Months later on:

Characteristic lines in the nails (Mees' lines), sensorimotor neuropathy.

hyperkeratosis of the palms and soles.

acute effects of arsenic poisining

Gastrointestinal
Violent gastroenteritis
Hematemesis/hematochezia
Jaundice
Pancreatitis
Dysphagia
Hepatomegaly

Cardiovascular
Third spacing with shock
Sinus/ventricular tachycardia
Prolonged QT interval, ST depression, T wave inversion
Torsades de pointes
Pericarditis

Respiratory
Respiratory failure
Adult respiratory distress syndrome
Pulmonary edema
Pneumonia

Renal
Proteinuria
Hematuria
Oliguria
Renal failure

Neurologic
Headache
Drowsiness
Delirium
Coma
Encephalopathy
Seizures

Diagnostic Strategies:

- Normal arsenic levels are

Blood: 5 micg/L

- Urine: less than 50 micg/day in a (24-hour urine)
- Any urine level above 100 micg/day or 50 micg/L necessitates treatment.

Management:

- Hemodialysis removes arsenic in the setting of acute renal failure.
- Exchange transfusions or plasma exchange should be considered very early after an arsine exposure

- No Activated charcoal, does not adsorb arsenic
- With a known history of exposure in asymptomatic patient, chelation should start as early as possible without waiting for laboratory confirmation of the arsenic levels.
- Intramuscular dimercaprol is the preferred chelator inpatients who are critically ill.

- DMSA is a water-soluble analogue of dimercaprol that can be given orally.

MERCURY (Hg) pathophysiology:

- The most familiar form of mercury is elemental or metallic mercury, also known as "**quicksilver**."
- A common route : inhalation of volatilized vapor.
- mercury is a common pollutant of air and water.
- After inhalation, 74% of the metallic mercury is retained in the lungs. This can result in severe pneumonitis and ARDS
- Aspiration of elemental mercury results in primary pulmonary toxicity, in addition to CNS and renal toxicities.
- ingestion does not normally lead to systemic toxicity unless it becomes trapped in diverticulae.
- <u>The organic mercury</u>

The major route of exposure to this type of mercury is through ingestion, but these compounds are also readily absorbed through the skin.

- These organic forms classically result in delayed neurotoxicity with prominent ataxia, tremor, dysarthria, and tunnel vision.
- <u>Inorganic mercury</u>

have two different forms: Hg^{1+} (*mercurous*) and Hg^{2+} (*mercuric*).

Ingestion of either salt leads to significant gastrointestinal and renal toxicity.

- Mercury binds sulfhydryl groups.
- Nephrotoxicity :direct damage and an immune reaction in the kidney.
- The skin changes: immune reaction.
- Mercury increases catecholamine level resulting in hypertension and tachycardia.
- Atrophy of the cerebellum.

Clinical Features:

- Inhalation of elemental mercury onset of shortness of breath, fever, and chills that progresses to pneumonitis and respiratory distress.
- Aspiration of liquid metallic mercury during medical procedures results in the rapid onset of tracheobronchial hemorrhage Acute ingestion of inorganic salts typically causes a corrosive gastroenteritis with third spacing and hemorrhage.
- Patients complain of a metallic taste in the mouth and may have a grayish discoloration of the mucous membranes.
- Massive fluid loss results in shock and acute tubular necrosis.
- Normal" mercury levels are considered to be
- Blood: less than 10 micg/L
- Blood level more than 35 micg/L needs Rx
- Chelation Therapy:
- BAL is used for clinically significant acute inorganic mercury intoxication
- DMSA :used for both acute and chronic
- d-Penicillamine is also used.
- It should be administered only after thorough gastrointestinal decontamination because mercury absorption from the intestinal lumen is enhanced by the penicillamines.

- Initial management in the acutely poisoned patient should be aggressive support and decontamination.
- Gastric lavage with protein-containing solutions (e.g., milk and egg whites) may be beneficial in the decontamination of the gastrointestinal tract following ingestion of mercury salts.
- Charcoal adsorbs very little and is not recommended
- Ingested metallic mercury is generally harmless unless its passage is impaired by entrapment in a diverticulum or the appendix.
- For acute inhalational exposures
- patient should be removed from the source
- supportive management provided.
- There is no role for prophylactic antibiotics or steroids.

Suction and postural drainage are indicated in cases of acute aspiration of metallic mercury.

Self-injection of metallic mercury often requires surgical debridement of infiltrated tissue

- BAL is used for clinically significant acute inorganic mercury intoxication.
- Because it increases brain mercury levels in patients with methylmercury poisoning, BAL is contraindicated for patients poisoned with organic mercury compounds.
- DMSA :used for both acute and chronic

mercury poisoning and may be the best chelator for methylmercury.

- d-Penicillamine is also used.

It should be administered only after thorough gastrointestinal decontamination because mercury absorption from the intestinal lumen is enhanced by the penicillamines.

- Type of questions in the exam:
- Whats the toxic level?
- Where is the substance available?
- How do you treat it?
- Whats the antidote?