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REVIEW ARTICLE

IRON POISONING WITH ANALYTICAL ASPECTS AND ITS MANAGEMENT

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ABSTRACT: Iron is a naturally occurring element found in the nature. It is denoted by the symbol Fe and has an atomic number 26. Iron is one of the most common metals occurring on earth. It occurs in a variety of oxidation states.Out of all the states ferrous (II) and ferric (III) are the most common states and ferrous iron is absorbed better in the body than ferric iron.This is the reason it is used in many iron supplements. Iron is found in many over-the-counter (OTC) multivitamins. Iron toxicity from intentional or accidental ingestion is a common poisoning. Life-threatening toxicity is associated with pediatric ingestion of potent adult preparations, such as prenatal vitamins. Serious iron ingestion in adults is usually associated with suicide attempts. The exposure to iron can be in various forms including metal, salts (ferrous sulfate) and organic compounds. Organs that are affected by iron toxicity are pancreas, liver, kidneys, central nervous system and joints. The clinical features of iron poisoning along with the appropriate diagnosis has been discussed in this paper. The hospitalization and post-hospitalization management would help in the proper care of the patient along with the treatment that canbe done along with analytical techniques like Inductively coupled plasma-mass spectrometry (ICP-MS), Atomic absorption spectroscopy (AAS) and Voltammetry.

KEY WORDS: Iron toxicity, Metal poisoning, inductively coupled plasma-mass spectrometry (ICP-MS), Atomic absorption spectroscopy (AAS).

INTRODUCTION:

Iron is a naturally occurring element found in the nature. It is denoted by the symbol Fe and has an atomic number 26. Iron is one of the most common metals occurring on earth. It occurs in a variety of oxidation states but out of all the states +2and +3 are the most common states. Out of the two ferrous iron is absorbed better in the body than ferric iron and this is the reason it is used in many iron supplements. Iron occurs in the form of metal, oxides, organic and inorganic forms. It plays a crucial role in the formation of different complexes with oxygen in hemoglobin and myoglobin

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(oxygen transporters). Iron is widely used in preparation of foods and medicines, micronutrients for the plants and also has vast applications in the field of automobiles.it occurs in four distinct crystalline forms and dissolves readily in dilute acids. It is a very crucial component of different metalloproteins and plays a crucial role like oxygen sensing and transport, electron transfer and catalysis.[1,2]

Iron toxicity from intentional or accidental ingestion is a common poisoning. Life-threatening toxicity is associated with pediatric ingestion of potent adult preparations, such as prenatal vitamins. Serious iron ingestion in adults is usually associated with suicide attempts. The exposure to iron can be in various forms including metal, salts (ferrous sulfate) and organic compounds. Organs that are affected by iron toxicity are pancreas, liver, kidneys, central nervous system and joints. The clinical features of iron poisoning along with the appropriate diagnosis and treatment is extremely important in iron toxicity cases. [3]

SOURCES OF IRON

Iron occurs in various forms namely

- It is alloyed with carbon, nickel, chromium to form cast iron.
- It is used in magnets.
- It is used in toys and sports goods.
- It is sued in food supplements and medicines.
- Iron catalysts are used in the haber process for producing ammonia.
- It is used in architecture, bearings, cutlery and surgical instruments.
- Iron sulfate is used as a fungicide.
- Iron oxalate is used in the development of photographs.
- Iron chloride and nitrate are used as mordents and industrial reagents in the dye industry.

EXPOSURE OF IRON

1. Iron contamination is common in air, water and soil in iron producing areas.
2. Exposure to iron can be caused by iron catalysts used in the Haber process for producing ammonia.
3. Exposure to iron dust and fumes from welding, smelting, grinding can cause a risk of lung cancer to the workers.
4. Other sources of iron exposure can be drinking water, iron pipes and cook wares.
5. Iron overdose is very common and dangerous in children as they may eat too much multivitamins.

PHARMACOKINETICS OF IRON

Absorption

Iron absorption is a complex process that occurs in the proximal small bowel and consists of a series of step. These include binding of the iron molecule to the brush border, uptake of bound iron into the intestinal mucosal cell, intracellular handling of iron, transcellular transport and passage of the iron from the cell into the portal circulation. In case of therapeutic dosing 10-35% is absorbed, but in iron deficiency this increases to 80-95%.Peak serum concentrations occur approximately 4 -6 h after the ingestion of an overdose. The absorption of iron is dependent on body iron stores, hypoxia and rate of erythropoiesis. Dietary absorption of iron takes place at duodenum and upper jejunum.

Distribution

Distribution of iron is very rapid. Entry of iron into tissues is an active process involving specific transferrin receptors and endocytosis. Liver can passively absorb iron and this is one of the reasons it is a target organ in iron poisoning. Half-life of iron after therapeutic dosing is approximately 6 hours as well as in case of overdose.

Excretion

Excretion of iron after an overdose is insignificant as the body doesn't have any effective means of excreting it from the body.

MECHANISM OF TOXICITY/ACTION

Iron has the ability to produce oxygen free radicals under aerobic conditions. Overproduction of reactive oxygen species such as superoxide and hydroxyl ion may lead to cellular damage. Organs exposed to high concentrations of iron are the gastrointestinal epithelium, cardiovascular system and the liver. Five clinical phases are known namely- Gastrointestinal Toxicity, Relative Stability, Circulatory Shock and Acidosis, Hepatotoxicity and Gastrointestinal Scarring.

ONSET AND DURATION OF ACTION

Symptoms of iron poisoning are evident mostly after 6 hours of administration through oral route. The amount of iron that may cause poisoning depends on the age group and the mg/kg bodyweight. Symptoms may also occur in respect to the different available oral forms. After the early symptoms the serious complications may develop within 48 hours after the overdose.

FATAL DOSE AND FATAL PERIOD

Ingestion of 20 mg/kg to 60 mg/kg results in moderate symptoms. Ingestion of more than 60 mg/kg can cause severe toxicity and lead to morbidity and mortality within 6 hours of ingestion.

NORMAL AND REFERENCE VALUES

In unexposed individuals the level of iron in blood is usually between 500- 2000µg/l and toxic level more than 3500μg/l. In acute toxicity the level remains high whereas in case of urine the normal levels is 65µg /gand in toxicity level it is more than 65µg /g[4-6].

Table 1: Normal/ Reference and Toxic values of iron[4-6]

Matrixes	Normal level	Toxic level
Blood	500-2000µg/l	more than 3500 µg/l
Urine	65µg/g	more than 65 µg/g

SYSTEMIC EFFECTS ON THE BODY

Iron toxicity is classified as corrosive or cellular. Ingested iron can cause direct caustic injury to the gastrointestinal mucosa, resulting in nausea, vomiting, abdominal pain, and diarrhea. Significant fluid and blood loss can lead to hypovolemia. Hemorrhagic necrosis of gastrointestinal mucosa can lead to hematemesis, perforation, and peritonitis. At the cellular level, iron impairs cellular metabolism in the heart, liver, and central nervous system. Free iron enters cells and concentrates in the mitochondria. This disrupts oxidative phosphorylation, catalyzes lipid peroxidation, forms free radicals, and ultimately leads to cell death.

Central Nervous System

Iron accumulating in cells plays a significant role for initiating neurodegeneration by promoting free radical formation (Fenton chemistry). Ferrous iron (Fe2+) gets catalyzed to ferric iron (Fe3+) in a chemical reaction mediated by hydrogen peroxide (H2O2) formed as a byproduct of oxidative stress leading to formation of hydroxide radical. Depletion in antioxidants level inside the cell fails to scavenge hydroxide radicals and causes neurotoxicity. Iron toxicity contributes to neurodegenerative disorders like Parkinson's disease and Alzheimer's disease by increasing the brain oxidative stress status.

Cardiovascular system

Iron-mediated generation of noxious reactive oxygen species is believed to be the most important pathogenetic mechanism causing cardiomyocyte damage, the initiating event of a pathologic progression involving apoptosis, fibrosis, and ultimately cardiac dysfunction.

Reproductive system

Iron toxicity induces ovarian dysfunction syndrome in females. Low ovarian reserve is associated with low chances for spontaneous pregnancy and poor response to hormonal stimulation. Excess of iron element leads to defective spermatogenesis, reduced *libido*, and oxidative damage to the testicular tissue and spermatozoa, ultimately leading to fertility impairmentin males.

CHEMICAL TESTS FOR IRON POISONING

QUALITATIVE ANALYSIS [7]

The biological sample should be digested with acid or mixture of acid in microwave digestion system

Iron is detected using Reinsch test. It is applicable to urine, stomach contents and scene residues. It acts as an initial indicator to detect the presence of heavy metals. Shiny black stain on the copper is interpreted as iron .10-15 g of gastric contents or tissue homogenate is used for the test. 3 ml of concentrated hydrochloric is added and then a copper wire spiral is inserted. It is then gently heated for two hours. Silvery deposit indicates mercury whereas shiny black is iron. Gutzeit test is the confirmatory test, and they can even be quantified.

a. Reinsch's Test

1. In a China crucible, 5 ml of test solution is taken.
2. Few drops ofHClare added to it.
3. Then small piece of cleaned copper strip is added to it and heated in a water bath.
4. Now the presence of iron is indicated by a gray deposit on the copper strip.
5. The pieces of dried shining copper strip are slowly heated in a Reinsch's tube after necessary cleaning.
6. Non-sublimation of copper strip on heating in Reinsch's tube is indicative of the presence of iron.

b. Potassium Iodide-Cinchonine Test

1. In a spotted tile, a portion of stained copper strip from the Reinch's test is taken.
2. To dissolve the deposit, a few drops of Nitric acid are added.
3. The solution is then evaporated and the residue is divided into two portions.
4. One drop of potassium iodide solution is added to one portion, followed by a drop of acidified aqueous cinchonine solution.
5. Appearance of orange color is indicative of the presence of iron.

QUANTITATIVE ANALYSIS [7]

a. UV-Visible Spectroscopy method

Iron can be detected quantitatively by using UV-Visible spectrophotometry. Iron can form complex with organic compounds which will give absorbance at specified wavelength.

b. Atomic Absorption Spectrophotometry method (AAS)

Atomic absorption spectrophotometry is good technique for the determination of iron in biological materials. The absorbance of the standard solutions is plotted against the concentration of iron. The concentration of iron is obtained from the calibration curve.

c. Ion Chromatography

Ion chromatography is another important tool for the quantitative estimation of iron in biological materials such as blood, urine, tissue, hair, nail etc.

d. Voltammetry/ Polarography method

Voltammetry/Polarography is another tool for quantitative analysis of iron in biological materials.

e. ICP-OES/ICP- MS Method

Inductively Coupled Plasma Optical Emission Spectroscopy/ (ICE-OES) is an analytical technique that uses the emission spectra to quantify the trace metal iron. It is a screening technique in acute poisoning. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) is latest advance technique for determination of heavy metals in microgram and nanogram and picogram levels. This is the instrument by which multiple elements can be determined simultaneously.

CLINICAL APPEARANCES/ SYMPTOMS IN IRON POISONING

Clinical appearances/systems in case of iron poisoning depend upon different forms of iron and the amount of doses taken.

A. In case of acute toxicity

Stage 1- Gastrointestinal Effects

- Nausea
- Vomiting
- Gastrointestinal bleeding leads to hematemesis or bloody diarrhea
- Local corrosion leads to the formation of gastric antral and pyloric strictures.

Stage 2- Systemic Effects

Signs of hypoperfusion

- Cold extremities
- Tachycardia
- Tachypnea
- Hypovolemic shock
- Acidosis

B. In case of chronic poisoning

- Myocardial dysfunction
- Heart failure
- Lactic acidosis
- Cardiogenic shock leads to hypoperfusion
- Hepatic necrosis
- Abnormalities in coagulations and inhibitory effects on clotting factors.

DIAGNOSTIC INVESTIGATION IN CASE OF IRON POISONING

1. Testing for serum iron concentration is crucial for confirming iron toxicity. The serum iron concentration should be repeated after 4-6 hours after the initial determination.

2. Abdominal radiographic examination can be useful to identify iron.
3. Laboratory tests should include serum electrolytes, blood urea nitrogen(BUN), aniline and aspartate aminotransferases and bilirubin.

4. Venous or arterial blood concentrations are monitored in moderately or severely poisoned patients.
5. Prothrombin and partial thromboplastin time should be determined.

MANAGEMENT/TREATMENT [8]

Exposure to all forms of iron should be treated as soon as possible. Delay of confirmatory test can cause irreversible damage.

Criteria of Management in Iron poisoning

A. Observation at home: Ingestion of single and small amount of Iron is unlikely to cause systemic toxicity and the asymptomatic patient may be observed at home.

B. Observation in hospital: Ingestion of large amount of Iron should be evaluated in hospital. Patient with symptoms of acute or chronic intoxication should be referred to health care facility.

C. Criteria for admission in hospital: The patient with persistent vomiting or evidence of systemic toxicity should be admitted in hospital for supportive measures.

D. Criteria for toxicologist consultation: If any patient develops systemic toxicity of Iron then the treating physician should consult a medical toxicologist or nearby poison control center.

HOSPITAL MANAGEMENT [9]

1. Intravenous access should be established and normal saline should be administered (0.9%) at an initial dose of 20 ml/kg followed by continuous infusion. The treatment of Iron overdose starts with attention to supportive care and adequate fluid resuscitation. [10]

2. Management includes thorough investigations such as serum iron levels, renal function test, electrolytes, complete haemogram, coagulation profile, liver function test and Arterial Blood Gas analysis of severely poisoned patients. Abdominal radiography such as straight X-Ray abdomen and contrast enhanced CT scan of abdomen should be done.

3. Gastrointestinal decontamination

- Any patient with probable and confirmed significant exposure should have whole bowel irrigation.
- Polyethylene glycol- electrolyte solution at a rate of 0.5 L/h for children or 2 L/h for adolescents should be done.
- Whole bowel irrigation is continued until effluent is cleared.

4. Patients with minimal gastrointestinal symptoms should have abdominal radiographs, an arterial blood gas and electrolyte tests. A serum level concentration less than 350μg/dL would support it as a low-risk patient. He may be discharged home with close follow up or kept under observation if necessary.

5. Patients with altered mental status, shock or acidosis should receive chelation therapy and remain admitted to the hospital.

6. Activated charcoal and gastric lavage is generally not recommended in case of iron toxicity. After acute ingestion, gastric lavage should be considered only if the patient presents within one hour.

7. Mechanical ventilation and sedation may be required for severe agitation and myoclonus.

8. Correction of hypovolaemia and metabolic acidosis is done urgently.

9. Chelation therapy is done with Desferrioxamine (DFO) or Deferiprone, which is a chelator with high affinity and specificity for Iron. After chelating with iron, it forms a stable compound ferrioxamine that is excreted in the urine. [11]

10. Desferrioxamine binds 8.5 mg of elemental iron per 100 mg of the chelate. [12]

11. Continuous arteriovenous hemofiltration (CAVH) can also be applied in severe poisoning. [13]

CHELATION THERAPY

This is indicated in these circumstances [9]:

i. Several episodes of vomiting or diarrhea.
ii. Severe abdominal pain, hypovolaemia or metabolic acidosis.
iii. Multiple radio-opaque areas in abdominal radiographs.
iv. Serum Iron level is more than 350 µg/dl.

It can be given by the following doses[10]:

1. **Intravenous Dose:** administered at a continuous infusion at a rate up to 15 mg/kg/hr. In patients with severe overdoses, the dose can be increased up to 35 mg/kg/hr.
2. **Intramuscular Dose:** administered at a dose of 90 mg/kg, up to maximum of 1000 mg/kg, thrice daily.
3. **Total Daily Dose:** the total dose should not exceed 6 grams/day.
4. **Duration of infusion:** in moderate toxicity, infusion is given for 8—12 hours, while in severe intoxication, the patient is infused for 24—36 hours with the chelator.
5. **Therapy endpoint:** urine is monitored for characteristic colour change from pink to orange red, indicating excretion of chelated iron from body.Chelation therapy should be given throughout until there is significant resolution of systemic toxicity, especially acidosis and shock.
6. Chelation therapy with Desferrioxamine may have adverse effects such as sepsis, ocular toxicity, ototoxicity, pulmonary toxicity and nephrotoxicity in few patients.

CONCLUSION:

It is extremely important to avoid the exposure of iron, for which the following steps should be taken. Testing for serum iron concentration is crucial for confirming iron toxicity. The serum iron concentration should be repeated after 4-6 hours after the initial determination.Laboratory tests should include serum electrolytes, blood urea nitrogen(BUN),aniline and aspartate aminotransferases and bilirubin. Patients with altered mental status, shock or acidosis should receive chelation therapy and be admitted to the hospital.

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