PHARMACOTHERAPY IN IRON DEFICIENCY ANEMIA

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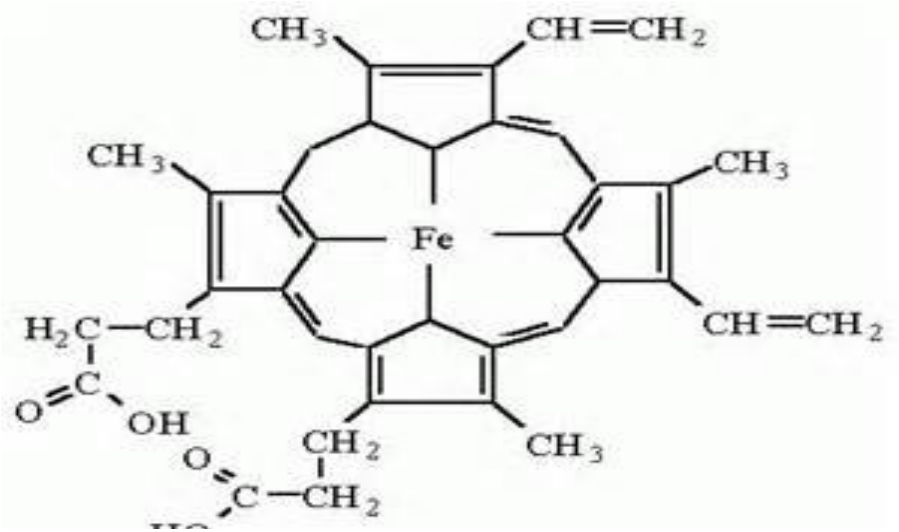
LEARNING OBJECTIVES

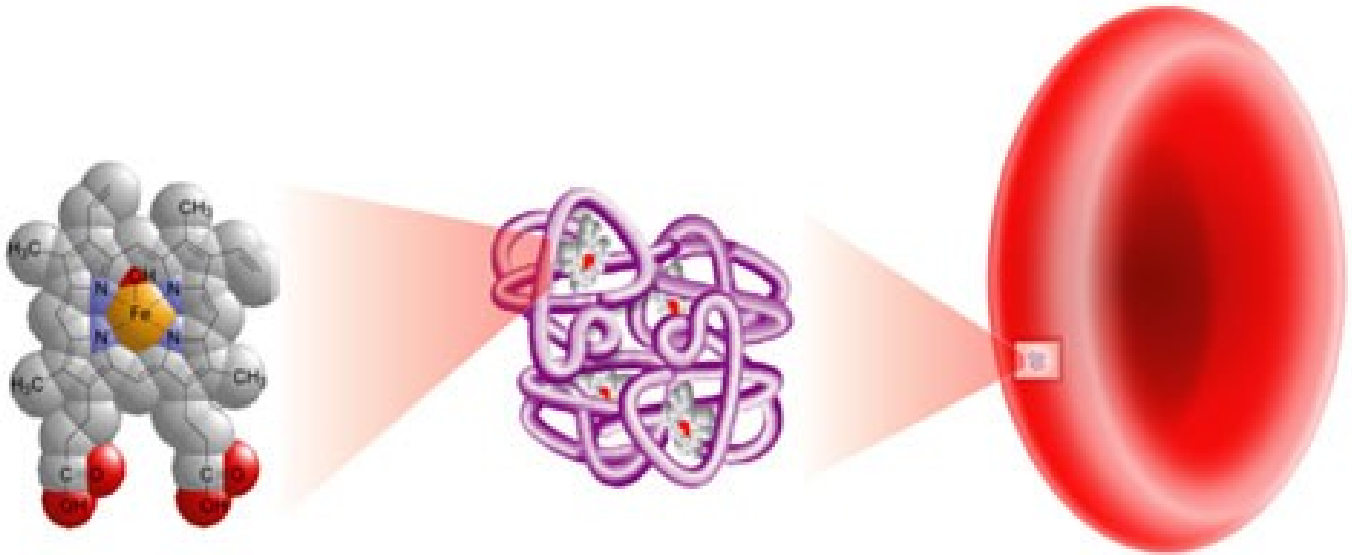
- Classify the drugs used in anaemia
- Describe pharmacokinetics of Iron
- Describe the various oral and parenteral formulations of iron
- Describe the adverse effects of iron therapy
- Describe the drug treatment of Iron toxicity

IRON

Iron forms the nucleus of the iron- porphyrin heme ring, which together with globin chains forms **hemoglobin**.

Hemoglobin reversibly binds oxygen and provides the critical mechanism for oxygen delivery from the lungs to other tissues.

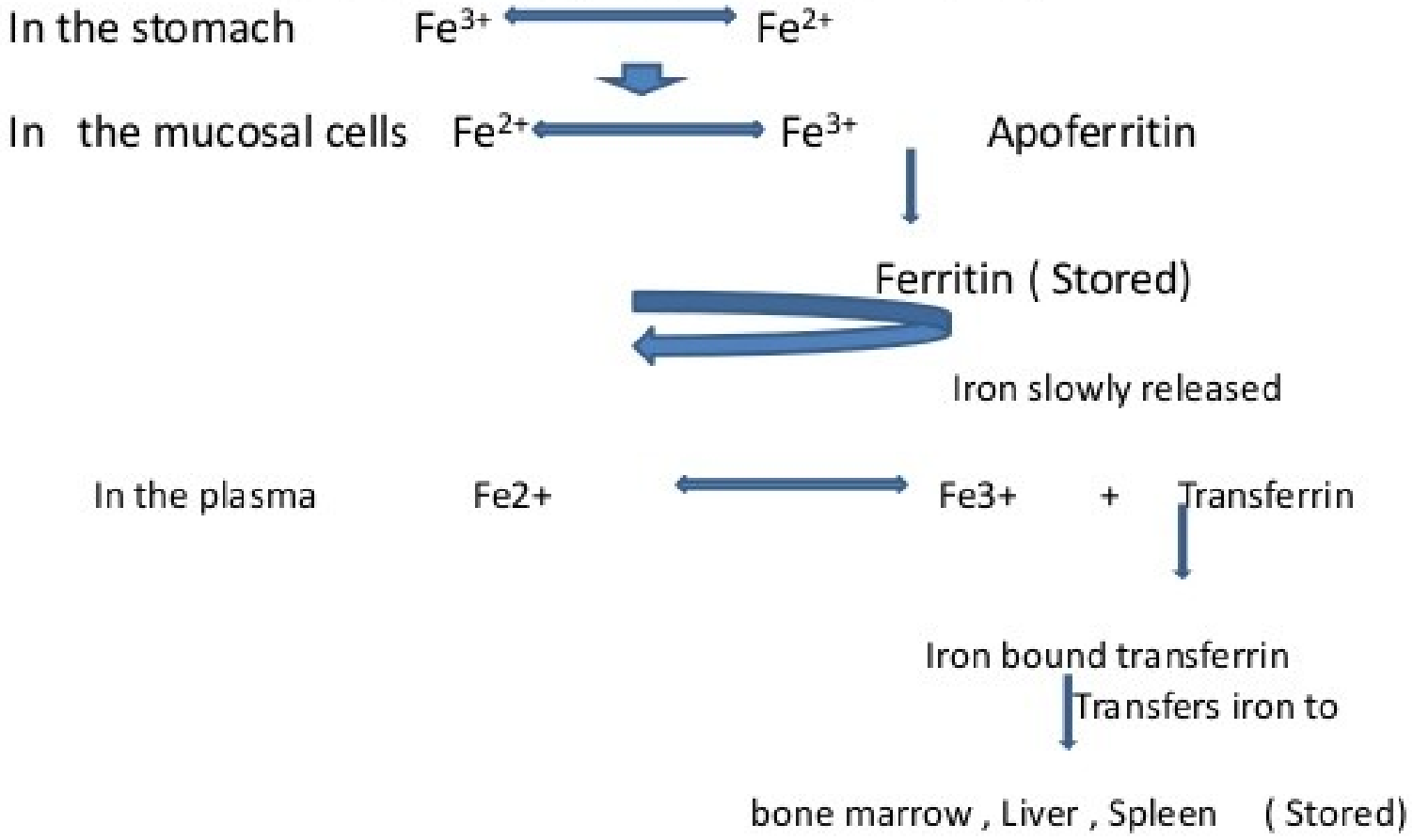

CH3
CH=CH2
CH3
CH3
Fe
H2C—CH2
CH=CH2
O=C
OH
CH2
CH3
O=C—CH2


Heme
Hemoglobin
Erythrocyte

Pharmacokinetics of iron

- Iron absorbs by active transport across intestinal mucosa.
- Converted Fe^{2+} to Fe^{3+}
- Apoprotein-iron complex (ferritin)
- Release on demand
- Absorption depends on apoprotein to ferritin ratio.
- Transferrin binds with free Fe^{2+} or Fe^{3+} from ferritin and carries to bone marrow

- Pharmacokinetics
  - Dietary iron mostly in the ferric form (Fe^{3+})



TYPES OF ANEMIA

Normochromic normocytic

- Anemia of chronic disease
- Hemolytic anemia
- Aplastic anemia

Normochromic macrocytic

- Vitamin B12 deficiency
- Folate deficiency

Hypochromic microcytic

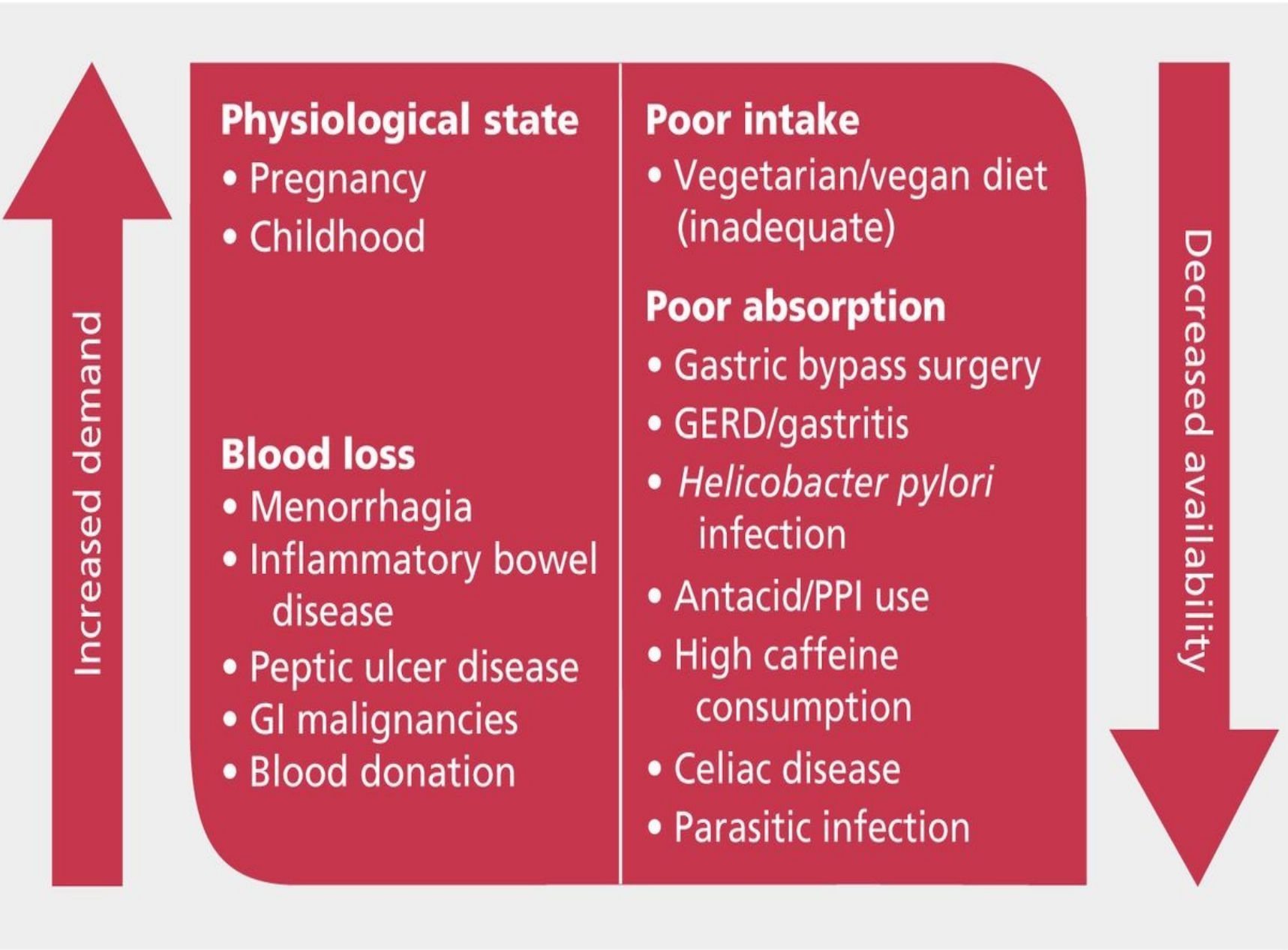
- Iron deficiency
- Thalassemia
- Anemia of chronic disease

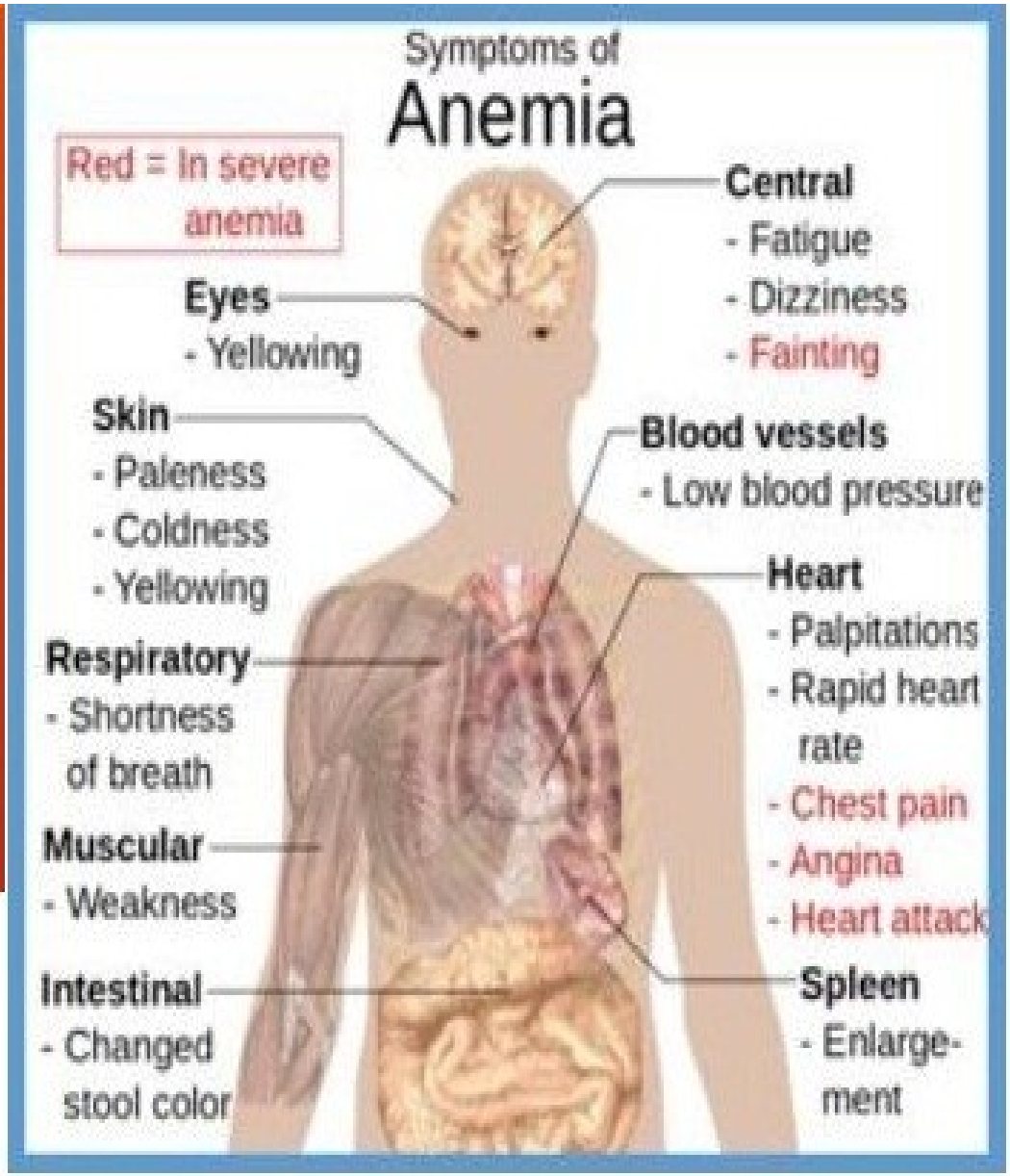
IRIDA (**I**ron-**R**efractory, **I**ron-**D**eficiency **A**naemia)
Case-Reports

Treatment

- Oral iron administration is ineffective
- Response to parenteral iron administration is partial
- Anaemia becomes less severe in adulthood as a consequence of the greater availability of the limited amount of available iron to erythropoiesis

Melis MA, et al. *Haematologica*. 2008 Jul 4. [Epub ahead of print] PMID: 18603562.


Increased demand
Physiological state
• Pregnancy
• Childhood
Blood loss
• Menorrhagia
• Inflammatory bowel disease
• Peptic ulcer disease
• GI malignancies
• Blood donation
Poor intake
• Vegetarian/vegan diet (inadequate)
Poor absorption
• Gastric bypass surgery
• GERD/gastritis
• Helicobacter pylori infection
• Antacid/PPI use
• High caffeine consumption
• Celiac disease
• Parasitic infection
Decreased availability


Symptoms of
Anemia
Red = In severe anemia
Central
- Fatigue
- Dizziness
- Fainting
Eyes
- Yellowing
Skin
- Paleness
- Coldness
- Yellowing
Blood vessels
- Low blood pressure
Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack
Respiratory
- Shortness of breath
Muscular
- Weakness
Intestinal
- Changed stool color
Spleen
- Enlarge-ment

CLINICAL PRESENTATIO

SYMPTOMS

Decreased oxygenation

- Dyspnea, Fatigue, Lethargy, Confusion

Decreased volume

- Fatigue, Muscle cramps, Postural dizzine
- Syncope

CVS adaptations

- Palpitations
- PICA a compulsive eating **disorder** eat nonfood items. Dirt, clay, and flaking paint

PICA

- Compulsive eating disorder Syndrome
- Eat nonfood items
- Commonly = Dirt, clay, and flaking paint
- Less common items include glue, hair, cigarette ashes, and feces
- More common in children= 10% to 30% of young children ages 1 to 6.
- Causes
  - Iron-deficiency anemia
  - Malnutrition
  - Pregnancy

SIGNS

- Pallor on mucous membranes and palm
- Koilonychia
- Glossitis
- Angular stomatitis
- Splenomegaly

IRON DEFICIENCY ANEMIA

Definition:

too low a body iron stores support RBC production

- Hemoglobin
  - Women <12
  - Men <13.5
- Hematocrit
  - Women <36
  - Men <41

PATHOPHYSIOLOGY

- Total iron body stores in 70 Kg adult man: 4 g
- A person with 5L of blood has 2.5 g of iron incorporated into Hb.
- Daily iron requirement : 20 – 25 mg
- Total daily intake : 10-15 mg
- Total daily absorption : 1 mg
- Daily iron destroyed 0.8%

MANAGEMENT

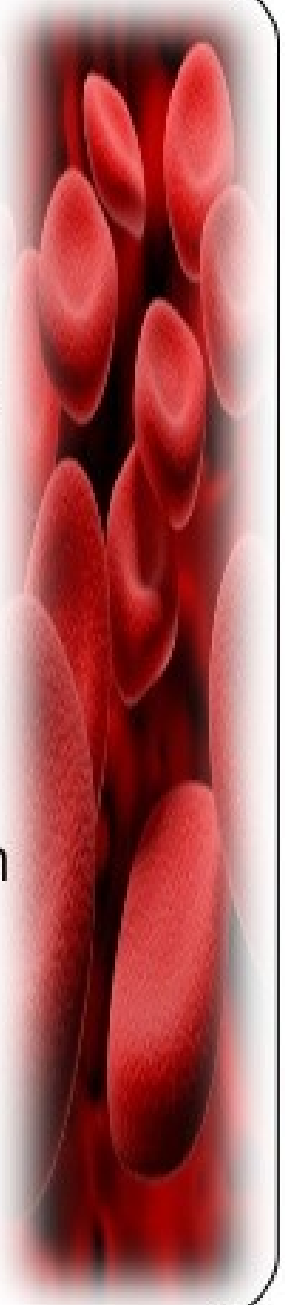
- Diet

Iron Deficiency Anemia

- **Treatment**
  - oral iron supplementation: 4 - 6mg/kg/day of elemental iron
  - goal: to replace iron stores, not just circulating Hgb!
  - Reticulocytes- starts to rise in 3 -4 days,
  - Hbg- after 4- 5 days
  - After Hgb normalisation – continue Fe therapy 1-2 months to replace Fe stores
  - *Iron- rich foods:
    animal protein, green vegetables, iron fortified cereales
  - Folate, vit C

TREATMENT OF IRON DEFICIENCY ANEMIA.

- Iron deficiency anemia is treated with oral or parenteral iron preparation. Oral iron corrects the anemia just as rapidly and completely as parenteral iron in most cases if iron absorption from the GIT is normal.
- Different iron salt provide different amount of elemental iron.
- In iron deficient individual, about 50-80mg of iron can be incorporated in hemoglobin daily and about 25% of oral ferrous salt can be absorbed.
- Oral iron treatment may require 3-6 months to replenish body stores.



INDICATIONS FOR THERAPY

Prevention of anemia

- Pregnancy
- Lactation
- Mennorhagia
- Patients with chronic renal disease
- Postoperative therapy

Treatment of anemia

IRON PREPARATIONS

- **Oral**

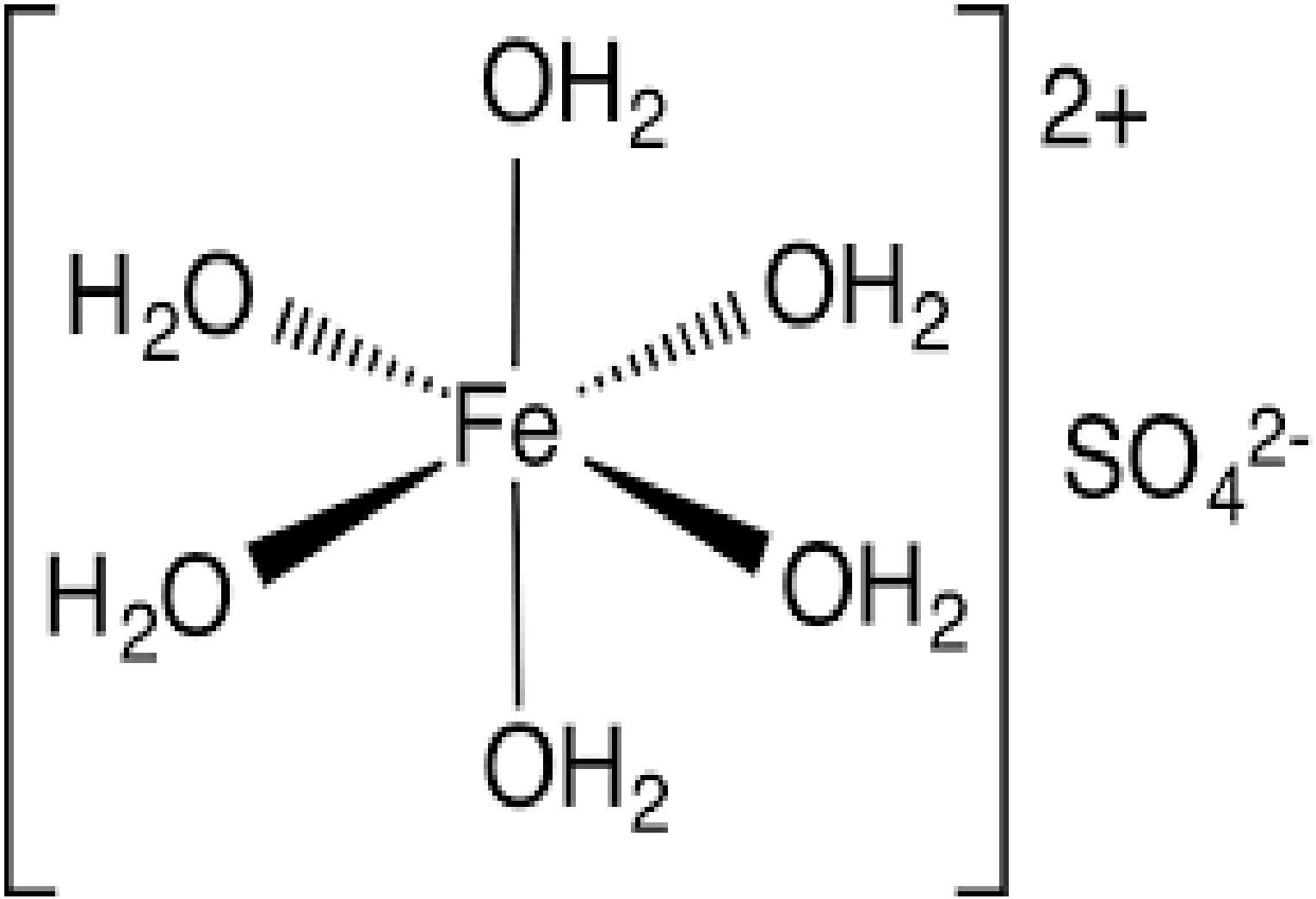
- Ferrous sulphate
- Ferrous gluconate
- Ferrous fumerate

- **Parenteral**

  - Iron dextran (IM/IV)
  - Iron sucrose(IV)
  - Sodium ferric gluconate(IV)
  - Iron Sorbitol

ORAL

HEMATINICS


OH2
H2O
OH2
Fe
H2O
OH2
OH2
2+
SO4 2-

Oral iron preparations

- Avoid enteric coated or SR iron
- Avoid giving with food
- 250 mg ascorbic acid enhances absorption
- Ferrous sulphate, fumarate gluconate equal efficacy and side effect profile
- Low dose as efficacious with fewer side effects
- Use in patients with IBD controversial

2. ORAL IRON THERAPY

- Adequate in asymptomatic patients with established anemia iron deficiency anemia
- Common used iron salts:
  - Ferrous sulphate (30% elemental iron tabs.)
  - Ferrous gluconate (12% elemental iron tabs.)
  - Ferrous fumarate (33% elemental iron tabs.)
- DOSE
  - 1 tab. 2 to 3 times a day
  - Ideally, in empty stomach since food inhibit absorption

PHARMACOKINETICS

Absorption…25%

- Promoters
- Inhibitors

Elimination

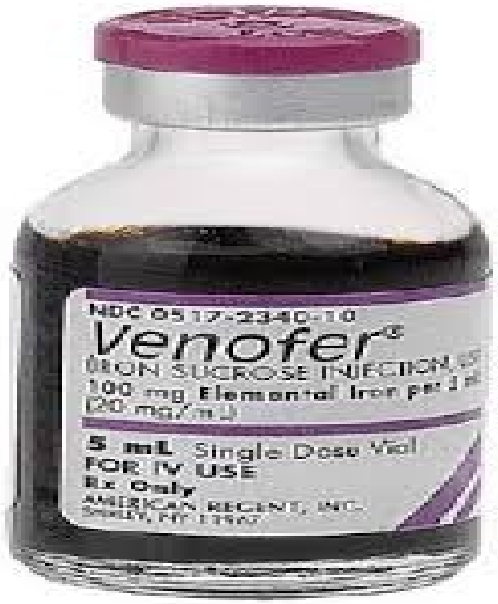
Duration of treatment

- 3-6months

ADVERSE EFFECTS (DOSE RELATED)

- Nausea
- Epigastric discomfort
- Abdominal cramps
- Constipation
- Diarrhea
- Black stools

PARENTERAL THERAPY



Compound	Recommended dosing/ administration	Test dose recommended*
Iron dextran	100–200 mg IV; or total dose IV replacement if <1,500 mg	Yes
Ferric gluconate	125 mg IV	Yes
Iron sucrose	200–250 mg IV	No
Ferric carboxymaltose	15 mg/kg IV to total of 1,000 mg	No
Ferumoxytol	510 mg IV	No
Iron isomaltoside	500 mg IV	No

PHARMACOKINETICS

- **TDI…**
- Total dose iron Dextran infusion
- Office one-stop therapy.

- **Calculations ==** Ganzoni formula

  Total **iron** dose =

  [actual body weight × (15-actual Hb)] × 2.4
  + **iron** stores)

Comparative properties of iron dextran and iron sorbitol

Iron dextran	Iron sorbitol
1. High molecular weight	1. Low molecular weight
2. I.M / I.V	2. I.M
3. I.M , 10 -30 % locally bound not available for immediate utilisation	3. Not locally bound
4. Not excreted	4. 30 % excreted in urine
5. I.M absorbed through lymphatics	5. Absorbed directly in circulation
6. Not bound to transferrin	6. Bound to transferrin may saturate it so very high free levels of iron in blood will be attained so not suitable for I.V administration
7. Taken up by macrophages and made slowly available to erythron	7. Directly available

Adverse effects

- Local pain & tissue staining
- Headache
- Light-headedness
- Fever
- Arthralgias
- Nausea, vomiting
- Hypersensitivity reactions

Duration of treatment

ACUTE IRON TOXICITY

Cause .....

Toxic doses:

- GI Toxicity: 20mg/kg
- Moderate toxicity: 40mg/kg
- Lethal toxicity: 60mg/kg

ACUTE IRON TOXICITY

CLINICAL PRESENTATION

- Vomiting, Diarrhea
- Abdominal cramps
- Shock
- Dyspnea
- Severe metabolic acidosis
- Coma, death

MANAGEMENT OF ACUTE IRON TOXICITY

- Gastric lavage
- General measures
- Iron chelation therapy

DEFEROXAMINE

- Source: Streptomyces pilosus
- MOA
  - ✓Binds free iron in blood
- DOSE
  - ✓100mg binds 8mg iron

CHRONIC IRON TOXICITY
(HEMOCHROMATOSIS)

- Cause
- Clinical presentation
  - Signs of heart failure
  - Signs of liver failure
  - Coma and death

Management

- Deferoxamine
- Deferasirox
  - High affinity for Fe^{+3}
  - Fecal excretion

Clinical Pharmacology

- **Parenteral iron therapy**
- Parenteral therapy should be reserved for
  - patients unable to tolerate or absorb oral iron
    - patients with various postgastrectomy conditions
    - patients with previous small bowel resection
    - inflammatory bowel disease
    - malabsorption syndromes
  - patients with extensive chronic blood loss who cannot be maintained with oral iron alone:
    - advanced chronic renal disease including hemodialysis and treatment with erythropoietin

REFERENCES

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