بسم الله الرحمن الرحيم

Treatment of Anemia (Part 2)

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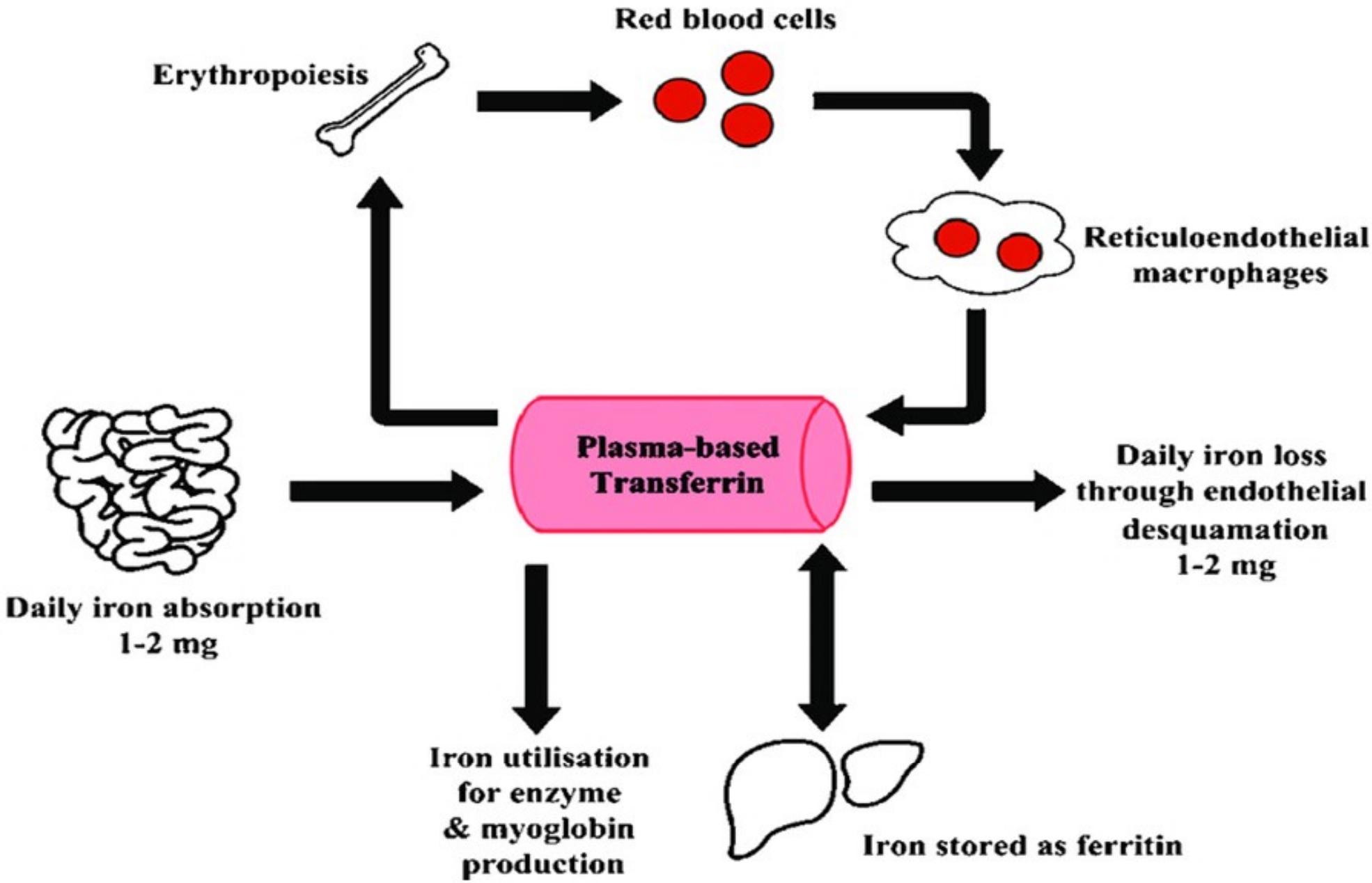
Pharmacokinetics of iron

1- Absorption

- Iron is available in several foods but is especially abundant in **meat.**
- The iron in meat protein can be efficiently absorbed, because heme iron in meat hemoglobin and myoglobin can be absorbed intact without dissociated into elemental iron.
- Iron in other foods, especially vegetables and grains, is often tightly bound to organic compounds and is much less available for absorption and must be reduced to ferrous iron (Fe^{2+}) before it can be absorbed by intestinal mucosal cells.
- Only 10 % of food's iron is absorbed.
- **Iron** is absorbed in the duodenum and proximal jejunum, although the more distal small intestine can absorb iron if necessary.
- The % of iron absorption increases in response to low iron stores (iron deficiency) up to 25%.



The % of iron absorption increases with increased iron requirements (e.g., iron absorption increases in menstruating women and reaches high rates in pregnant women).

2- Distribution:

Total body iron is about 3.5 gm.

- 10 % in myoglobin & enzymes,
- 20 % is stored in liver & reticuloendothelial system
- 70 % in hemoglobulin of RBCs.

3- Elimination of iron:

- There is no mechanism for excretion of iron.
- Small amounts are lost in the feces by exfoliation of intestinal mucosal cells, and trace amounts are excreted in bile, urine, and sweat.
- These losses account for no more than 1 mg of iron per day.
- Because the body's ability to excrete iron is so limited, regulation of iron balance must be achieved by changing intestinal absorption and storage of iron in response to the body's needs.

Pharmacological iron therapy

The only pharmacological indication for iron is the treatment of iron deficiency anemia (a hypochromic, microcytic anemia, in which the erythrocyte mean cell volume (MCV) and the mean cell hemoglobin concentration are **low**).

Causes of iron deficiency anemia

1- Physiological increase in iron requirements

A. **Infants** (esp. premature) and **children** during rapid growth periods.

B. **pregnant** and **lactating** women.

2- Decreased iron absorption: e.g., Patients with **malabsorption** and after **gastrectomy**.

3- Blood loss (the most common cause of iron deficiency in adults), examples:

A. Menstruating women lose about 30 mg of iron with each menstrual period. Many premenopausal women have low iron stores.

B. In men and postmenopausal women, the most common site of blood loss is the gastrointestinal tract. However, epistaxis, bleeding from gums or any other site could cause depletion of iron stores.

- **Patients with unexplained iron deficiency anemia should be evaluated for occult gastrointestinal bleeding (from peptic ulcer, malignancy, parasitic infection, etc.).**
- **The cause of bleeding should be treated.**

Pharmaceutical preparations of iron

- **oral** and **parenteral** iron preparations are avilable.
- Oral iron corrects anemia just as rapidly & completely as parenteral iron in most cases (if iron absorption from the GIT is normal).
  - ✓An exception is the **high requirement for iron** of patients with advanced chronic kidney disease who are undergoing hemodialysis and treatment with erythropoietin; for these patients, **parenteral iron administration is preferred.**

Oral iron therapy

❑ **Ferrous sulfate**, **ferrous gluconate**, and **ferrous fumarate** are effective and inexpensive oral iron preparations.

Duration of treatment:

Correction of anemia usually occurs within 2 months. Treatment must continue for 3-6 months after that to restore iron stores.

Factors affecting iron absorption:

1- Food may reduce the bioavailability of iron.

2- Antacids decrease its absorption.

3-Tea (tannins) precipitates iron, so it decreases its absorption.

4- Ascorbic acid (vitamin C) reduces ferric iron to ferrous iron, so it increases the absorption but may increase the side effects of iron which limits its benefit.

Oral iron dosing

✓In an iron-deficient individual, about 50–100 mg of iron can be incorporated into hemoglobin daily, and about 25% of oral iron given as ferrous salt can be absorbed.

✓Therefore, **200–400 mg of elemental iron should be given daily** to correct iron deficiency most rapidly.

✓Patients could be unable to tolerate such large doses of iron.

✓lower daily doses of iron, can be used instead which results in slower but still complete correction of iron deficiency.

Example: A 200 mg of ferrous sulphate tablet contains about 60 mg of elemental iron; only 25 % is absorbed (15 mg), so giving 2-3 tablets / day can provide the body with nearly **30-45 mg of iron / day.**

Adverse effects of oral iron therapy

1- GIT disturbances: **nausea**, **epigastric discomfort**, abdominal **cramps**, **constipation (common)**, and diarrhea (occasionally). These effects are usually **formulation** & **dose-related** and often can be overcome by lowering the daily dose of iron or by **taking the tablets immediately after or with meals**, and without dairy.

2- Patients taking oral iron commonly develop **black stools**; this has no clinical significance but may obscure the diagnosis of continued GIT blood loss.

Causes of failure of oral iron therapy:

1-Patient non-compliance.
2- Incorrect diagnosis.
3- Poor absorption.
4- GIT blood loss.

Parenteral iron therapy

1. **Iron dextran**
2. **Sodium ferric gluconate complex**
3. **Iron sucrose.**

Parenteral therapy should be reserved for:

1-Patients with **severe** documented iron **deficiency**.

2- Patients who couldn't **tolerate** or **absorb** oral iron.

3- Patients with advanced **chronic renal disease** requiring hemodialysis and treatment with erythropoietin.

4- Some patients with inflammatory bowel disease of the proximal intestine, post-gastrectomy, small bowel resection, and malabsorption syndrome.

- The pharmaceutical preparations of parenteral iron are composed of a **core of iron** surrounded by **a core of carbohydrate**, where the bioactive iron is released slowly from the carbohydrate core.
- If inorganic free ferric iron is injected (without a carbohydrate core); serious dose-dependent toxicity occurs.

Iron dextran

- ❑ Given **deep IM injection** or by **IV infusion** (used most).

Intravenous administration eliminates the local pain and tissue staining that often occur with the intramuscular route.

- ✓ High and low molecular weight forms of iron dextran formulations are used clinically.

Adverse effects of intravenous iron dextran therapy include:

- ❑ Headache, fever, arthralgias, vomiting, back pain, **flushing**, urticaria, bronchospasm, & rarely, **anaphylaxis** and death.
- ❑ To avoid anaphylaxis (small test dose is given before therapy).
- ❑ the risk of anaphylaxis is largely associated with high molecular weight formulations of iron dextran.

- ❖ For patients treated chronically with parenteral iron, it is important to monitor the iron storage levels (the transferrin saturation) to avoid the serious toxicity associated with iron overload.

Acute Iron Toxicity

- Acute iron toxicity is seen almost exclusively in young children who accidentally ingest iron tablets.
- As few as **10 tablets** of any of the commonly available oral iron preparations can be lethal in young children.
- Adult patients taking oral iron preparations should be instructed to store tablets in childproof containers out of the reach of children.
- Children who are poisoned with oral iron experience necrotizing gastroenteritis with vomiting, abdominal pain, and bloody diarrhea followed by shock, lethargy, and dyspnea. Subsequently, improvement is often noted, but this may be followed by severe metabolic acidosis, coma, and death.

Treatment of acute iron toxicity

- Urgent treatment is necessary.

1- Whole bowel irrigation should be performed to flush out unabsorbed pills.

2- Appropriate supportive therapy for gastrointestinal bleeding, metabolic acidosis, and shock must also be provided.

3- Specific treatment by IV Deferoxamine, a potent iron-chelating compound, that binds iron from tissues to promote its excretion in urine and feces.

- N.B. Activated charcoal, a highly effective adsorbent for most toxins, does not bind iron and thus is ineffective.

Chronic Iron Toxicity

Chronic iron toxicity can cause excessive iron deposition in the heart, liver, pancreas, and other organs. It can lead to organ failure and death.

Causes:

1- The inherited excessive iron absorption (hemochromatosis).

2- Individuals with β thalassemia who receive many red cell transfusions over a long period of time.

- ✓ Chronic iron overload is most efficiently treated by intermittent phlebotomy. About one unit of blood can be removed every week until all of the excess iron is removed.

- ✓ Iron chelation therapy is less efficient, more complicated, expensive, and hazardous

Injectable Iron chelators

1- Deferoxamine

Deferoxamine (chemical antagonism) chelates the free iron (non-transferrin bound iron), hemosiderin, and ferritin. It also chelates aluminum. It may be given IV, IM or SC.

It can't chelate the iron in cells (e.g., hemoproteins & cytochromes).

Uses:

1- Deferoxamine (intravenous) is the parenteral chelator of choice for acute iron poisoning.

2- Treatment of spontaneous intracerebral hemorrhage (reduces the brain iron overload resulted from hemoglobin breakdown).

3- Deferoxamine plus hemodialysis may also be useful in the treatment of aluminum toxicity in renal failure.

Adverse effects of deferoxamine

1- The iron-deferoxamine complex is excreted in the urine, often turning the urine an orange-red color.

2- Rapid IV administration may result in hypotension. flushing, abdominal discomfort, and rash.

3- Acute respiratory distress syndrome: deferoxamine infusions lasting longer than 24 hours.

4-Neurotoxicity and increased susceptibility to certain infections (e.g., with Yersinia enterocolitica) have been described after long-term therapy of iron overload conditions (e.g., thalassemia major).

2-Dexrazoxane

Dexrazoxane is an IV iron chelator that binds free iron removes iron from the doxorubicin-iron complex, thereby preventing oxygen free radical formation and reduces some of the cardiotoxic effects of doxorubicin.

Oral iron chelators

1- Deferasirox is orally absorbed. In the circulation, it binds iron, and the complex is excreted in the bile.

Deferasirox is used for long-term treatment of iron overload caused by repeated blood transfusions (for treatment of thalassemia and myelodysplastic syndrome).

- Monitoring of liver and renal function is advised during treatment of older adults with myelodysplastic syndromes.
- Adverse effects: gastrointestinal disturbances and skin rash.

2- Deferiprone, an oral iron chelator cleared predominantly via the kidney, was approved as a second line oral chelator for blood transfusion induced iron overload (in thalassemia).

- Regular hematologic monitoring is recommended because neutropenia and agranulocytosis may occur in some patients.


THANK YOU