THERAPEUTICS OF IRON DEFICIENCY ANEMIA;
FACTS AND FICTION

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Iron deficiency anemia is the most common deficiency disorder which afflicts Man. It shows global prevalence although there is a strong bias in favor of the lower socio-economic strata\textsuperscript{1}. Chronology and sex also dictate the demography of iron deficiency anemia\textsuperscript{2-3}. Because of its global prevalence in a large section of world population, iron deficiency anemia is one of the commonest ailments which a physician has to manage\textsuperscript{4}. Whereas the principles of the treatment of iron deficiency anemia are well established, their application calls for a critical re-appraisal\textsuperscript{5}. There are many disinformations about the treatment of iron deficiency anemia not only among the masses but also among some practicing physicians\textsuperscript{7,8,9}. The object of this presentation is to shed light on certain grey areas in the management of iron deficiency anemia. Some of these are:

1. Dietary iron
2. Milk and iron
3. Oral ferrous iron supplements
4. Oral ferric iron supplements
5. Parenteral iron therapy
6. Iron therapy in rheumatoid arthritis
7. Role of vitamin A, vitamin C and tea

1. DIETARY IRON:

Iron is present in most of the dietary items either as a contaminant or as an integral part of their composition. The amount however is rather small and even a well balanced diet barely contains 12-15 mg of elemental iron (6 mg / 1000 Calories).

Dietary items which are rich in iron include meat, apples, pears, dates and spinach. Meat iron is mostly in the form of hemoglobin and myoglobin. It is for this reason that red meat is a better source of iron than white meat. Whereas spinach is rich in iron, its benefit to the host is comparatively small. This is because phytates, sulphates, carbonates and phosphates present in the spinach adversely affect its absorption. Hence spinach is an unsatisfactory source of bio-available iron despite its high iron content.

Cow’s milk as well as human milk are poor sources of iron. One liter of milk contains a maximum of 1 mg of iron. Cereals also have a very low iron content. Infants who are breast fed or whose dietary supplements are mostly unfortified cereals are the prime targets for developing iron deficiency anemia.

Whereas a well balanced diet in an affluent society has enough iron for an adult male, it is almost impossible to supply the requisite amount of iron through diet alone to women during their reproductive years and in children and adolescents with increased iron demand to match their accelerated growth\textsuperscript{10}. A common belief and practice is to increase the intake of liver, spinach and apples to meet the additional iron demand under these circumstances; this is ill founded, ineffective and insufficient. Table\textsuperscript{11} summarizes body’s requirements of iron in the two sexes and at different ages.

<table>
<thead>
<tr>
<th></th>
<th>Obligatory loss</th>
<th>Menses</th>
<th>Lactation</th>
<th>Pregnancy</th>
<th>Rapid growth</th>
<th>Total daily requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Male</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Post-menopausal females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Menstruating females</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Adult Male</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pregnant females</td>
<td>1</td>
<td></td>
<td></td>
<td>1-2</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Children</td>
<td>0.5-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Note: All values in this table are in mg per day.

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2. MILK AS A SOURCE OF IRON:

Whereas milk has long been popular as a complete diet for children, it is not entirely so. Cow’s milk contains only 1 mg of iron per liter; human milk is not any better. Human milk, besides being a poor source of iron, may cause iron deficiency anemia in children in more than one ways:

a. It impairs the absorption of food iron as well as medicinal iron because of the presence of phosphates and calcium.

b. It is at times associated with ‘lactose intolerance’ which induces diarrhea; this is detrimental to adequate iron absorption.

c. Some children develop non-lactose milk allergy which produces bleeding spots in the gastro-intestinal mucosa. This aggravates the already existing iron deficiency state in children.

Infants who are fed on breast milk alone for more than six months are likely to develop the well described ‘milk anemia of childhood’.

3. ORAL FERROUS IRON SUPPLEMENTS:

Iron salts in ferrous form have traditionally been the backbone of treatment of iron deficiency anemia. These are at times associated with significant G1 intolerance to the point where some patients refuse to take iron by mouth. Many physicians under these circumstances recommend taking iron preparations with meals, milk or antacids to minimize the iron-associated G1 intolerance. This defeats the purpose of iron therapy as the absorption of medicinal iron, when taken with food, milk or antacids is greatly reduced. If a patient experiences G1-intolerance with one iron preparation, it is advisable to prescribe other preparations in lower doses to be taken at longer intervals before considering parenteral iron therapy. A better strategy is to take iron supplements 1-2 hours after meals. This confer the following advantages:

i. There is still some food in the stomach to prevent focal concentration of iron and to minimize gastric mucosal irritation.

ii. There is some free hydrochloric acid in the stomach so that the gastric pH is in the acidic range. This facilitates the absorption of food iron as well as the medicinal iron in the upper small intestine.

Some physicians prescribe oral iron to patients who are already on long term H2 receptor blockers or proton-pump inhibitors. H2 receptor blockers and proton pump inhibitors effectively block the secretion of hydrochloric acid in the stomach and impair the absorption of non-heme iron in the diet as well as the conventional iron supplements. Long term administration of these drugs is likely to affect body’s iron stores adversely. Oral administration of non-absorbable antacids impairs iron absorption by binding with food iron and rendering it unavailable for absorption. Non-absorbable antacids are therefore likely to induce a negative iron balance if administered over a long period.

4. ORAL FERRIC IRON PREPARATION:

Traditionally only the ferrous salts are administered as medicinal iron for the treatment of iron deficiency anemia. This is because the academic teaching has always been that ferric salts are poorly absorbed. Recently a new breed of oral iron preparations has been introduced. These contain ferric iron in the form of ferric hydroxide complexed with polymaltose. Advantages claimed by the manufacturers are many; some of these are:

i. Better absorption

ii. No staining of teeth

iii. Greater hematopoietic response!

iv. Lower incidence of G1-intolerance

v. Convenience of administration; unrelated to meals

vi. No generation of free radicals during transmucosal passage hence lower incidence of lipid peroxidation and reduced atherogenesis.

Like all newly introduced drugs, claims for ferric hydroxide polymaltose complex preparations are also tall. Their therapeutic efficacy, incidence of side effects and consumer acceptability shall have to await the test of the time. One major disadvantage is the comparatively higher cost of these preparations as compared with inorganic iron compounds.

Some of these preparations, their formulation and dosage in children as well as in adults are listed in table:

<table>
<thead>
<tr>
<th>PREPARATION</th>
<th>COMPOSITION</th>
<th>IRON CONTENT</th>
<th>DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A; Tablets</td>
<td>Ferric hydroxide - polymaltose complex</td>
<td>100mg</td>
<td>1-3 chewable tablets</td>
</tr>
<tr>
<td>• Apofer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ferosoft</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Apofer F</td>
<td>Ferric hydroxide - polymaltose complex + 350 ug folic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ferosoft FA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Syrups</td>
<td>Ferric hydroxide - polymaltose complex</td>
<td>50mg / 5 ml</td>
<td>1-2 teaspoonful*</td>
</tr>
<tr>
<td>• Rubifer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ferosoft</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ferplex</td>
<td>Ferric hydroxide - protein succinylate</td>
<td>13.5 mg / 5 ml</td>
<td>1-2 teaspoonful*</td>
</tr>
</tbody>
</table>

Table 2: Oral ferric iron preparations

* According to the age of the child
5. PARENTERAL IRON PREPARATIONS:

A. INTRAMUSCULAR:

Jectofer and Jectofer plus are the only two iron preparations which are currently available for intramuscular use\textsuperscript{11-12}. Previously available imferon (Iron dextran) has been abandoned. In order to raise Hb by 1 g/dl in an adult male, 150 mg of elemental iron as Jectofer or Jectofer Plus is required. Dose for children is proportionately less. All oral iron supplements should be discontinued at least 24 hours prior to Jectofer injection. This is to ensure that enough unsaturated iron binding protein is available to latch on to the injected iron as it enters the circulation and no free iron is left to generate free radicals and cause cellular damage. Jectofer must not be given intravenously nor it is recommended for total dose infusion.

B. INTRAVENOUS:

An intravenous iron preparation which has recently been introduced is venofer. Chemically it is ferric hydroxide complexed with sucrose\textsuperscript{13}. Comparative analysis of venofer and other parenteral iron preparations is given in table 3:

In order to raise hemoglobin to the desired level, the dose of Venofer iron may be calculated according to the following formula:

\textbf{TEST DOSE FOR PARENTERAL IRON:}

Sensitivity to parenteral iron must be tested by injecting a small amount of iron preparation by the same route as is contemplated for subsequent iron administration. Subcutaneous injection of iron as a measure of sensitivity testing is strictly forbidden.

The following are some of the indications for parenteral iron administration:

- Peptic ulcer disease
- Ulcerative colitis
- Crohn’s disease
- Ischemic colitis
- Bleeding hemorrhoids
- Isolated malabsorption of iron

Another group of disorders that also requires parenteral iron therapy includes unavoidable, persistent and chronic iron loss of such magnitude as cannot be met by oral administration of iron. These are:

- Non-compliant patient
- Intestinal angiodysplasia
- Cardiac hemolytic anemia
- Paroxysmal nocturnal hemoglobinuria
- Hereditary hemorrhagic telangiectasia

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Imferon</th>
<th>Jectofer</th>
<th>Jectofer Plus</th>
<th>Venofer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Iron dextran</td>
<td>Iron sorbitol citric acid</td>
<td>Iron sorbitol citric acid / folic acid 75 mg &amp; vit-B\textsubscript{12} 75 mcg</td>
<td>Iron sucrose</td>
</tr>
<tr>
<td>Formulation</td>
<td>2 ml &amp; 5 ml</td>
<td>1.5 ml</td>
<td>1.5 ml</td>
<td>5 ml</td>
</tr>
<tr>
<td>Iron content mg/ml</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Dose in mg to raise Hb by 1 g/dl</td>
<td>300</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Administration</td>
<td>I/M, I/V and I/V infusion</td>
<td>I/M only</td>
<td>I/M only</td>
<td>I/V infusion only</td>
</tr>
<tr>
<td>Absorption</td>
<td>Slow</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Immediate</td>
</tr>
<tr>
<td>Total dose infusion</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Availability</td>
<td>Obsolete</td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
</tr>
<tr>
<td>Cost in rupees / ampoule</td>
<td>N/A</td>
<td>20</td>
<td>20</td>
<td>250 +</td>
</tr>
</tbody>
</table>

Table 3: Comparative analysis of parenteral iron preparations
Parenteral administration of iron has a number of advantages; some of these are:

1. It obviates patients’ non-compliance

2. It assures ‘unlimited’ supply of iron to match the ‘unlimited iron loss’ in PNH, cardiac hemolytic anemias, hereditary hemorrhagic telangiectasia and intestinal angiodysplasia.

3. It can be given with impunity to patients with bleeding and ulcerating lesions in the gastro-intestinal tract

4. It enables iron supplementation in patients with selective malabsorption of iron.

There is a general belief that parenteral iron therapy hastens the hematological response. This is not true. Hematological response with parenteral iron therapy is similar to one with oral iron therapy in its onset, peak and the ultimate response. The only real benefit of parenteral iron therapy is the assured iron administration. Parenteral iron should therefore not be given with the expectation of early and higher therapeutic response.

5. IRON THERAPY IN RHEUMATOID ARTHRITIS:

Iron deficiency anemia in rheumatoid arthritis is not uncommon. This is caused by a multitude of factors including analgesic gastropathy resulting in chronic, persistent and sub-clinical blood loss from the upper gastrointestinal tract. Another important mechanism is the reticuloendothelial system hyperplasia in rheumatoid arthritis. RES hyperplasia and increased phagocytic activity causes excessive uptake and intracellular retention of iron which is not released from the macrophages as in normal individuals. Failure to release iron causes functional iron deficiency and microcytic and hypochromic anemia in patients with rheumatoid arthritis. These patients do not respond to oral iron supplements. Parenteral iron induces a hematological response by ‘mass effect’. As serum iron level increases rapidly after parenteral administration; some of it becomes attached to transferrin to be delivered to the bone marrow for effective erythropoietic response.

6. ROLE OF VITAMIN-A, VITAMIN-C AND TEA:

Administration of vitamin A to children with iron deficiency anemia was popularized as a means of reducing the incidence of infectious diseases. The data has not been convincing. On the contrary there is some suggestion that vitamin A actually increases the incidence of infections.

Vitamin C is a potent antioxidant and a powerful reducing agent. Administration of 500 mg of Vitamin C with oral inorganic iron preparations promotes iron absorption by maintaining the ferrous state of iron in the upper small intestine over a longer period.

Consumption of large quantities of tea impairs iron absorption by forming insoluble and non-absorbable ferric tannate in the stomach. Advantage is taken of this property to retard iron absorption in patients with chronic hemolytic anemias particularly thalassemia major and congenital dyserythropoietic anemias. Desferrioxamine, an iron chelating agent, also impairs iron absorption if administered orally; the amount of iron chelated is very small and is no clinical significance.

Recently the concept of one tablet of inorganic oral iron administrated over a longer period has been forwarded. This is claimed to be as effective in the ultimate rise in hemoglobin level. Also because of lower concentration, the incidence of gastric disturbance is decreased and the rate of patients compliance is enhanced.

From the foregoing it may be clear that whereas iron supplementation is an essential therapeutic modality for the treatment of iron deficiency anemia, its administration requires some expertise and awareness of the pros and cons of the available modes of iron therapy.

Total calculated dose of Venofer is administered in fractional doses intravenously daily, or at convenient intervals. The dose is diluted in 100ml of normal saline and is infused slowly over 1-2 hours, taking full precautions to combat any untowards reactions. Venofer must not be given by intramuscular injection. It should also not be administered as ‘total dose infusion’.

Intramuscular iron in general and intravenous iron preparations in particular should not be given in an office set up. They should always be given in a hospital where facilities are available to combat any untowards effects, particularly the hypersensitivity type of reactions. This is especially important for the first injection which also serves as the ‘test dose’. 
Hb deficit = Target hemoglobin – patients hemoglobin
Total iron deficit in mg = 
a. Hb iron deficit in mg = 
   Body weight in Kg x Hb deficit in g/dl x 0.24 
+ 
b. Storage iron deficit in mg
This is shown in the table below:

<table>
<thead>
<tr>
<th>Sex</th>
<th>&lt;40 kg</th>
<th>&lt;40 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target Hb G/dl</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Storage iron in mg</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target Hb G/dl</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Storage iron in mg</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

Derivation of factor 0.24:
0.24 = 0.0034 x 0.07 x 1000
0.0034 = Iron content of hemoglobin/dl
0.07 = Blood volume in relation to body weight
1000 = Conversion of grams to milligrams

REFERENCES