Meet the Expert

How to Choose a Right Oral Iron Preparation?

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Hall G
8.00 to 9.30 hrs.

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Iron Deficiency Anemia in Clinical Practice

Methods to treat iron deficiency
- Oral preparations
- Parenteral preparations
- Dietary iron
- Blood transfusion

Comparison of different methods of iron therapy

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Cost</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral FeSO4</td>
<td>Excellent</td>
<td>Cheap</td>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td>Parenteral</td>
<td>Good</td>
<td>Expensive</td>
<td>Fever, rash, joint pain, shock, death</td>
</tr>
<tr>
<td>Dietary iron</td>
<td>Mediocre</td>
<td>Expensive</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>Good</td>
<td>Expensive</td>
<td>TTI - HIV, hepatitis, fever, shock, death</td>
</tr>
</tbody>
</table>

Therapeutic oral iron preparations
- Preparations of iron salt
  - Ferrous sulfate
  - Ferrous fumarate
  - Ferrous gluconate
  - Ferrous glycine sulfate
  - Ferrous succinate
  - Ferrous calcium citrate
  - Ferrous amoniate
  - Ferric ammonium citrate
  - Ferrous ascorbate
  - Iron polysaccharide complex (iron polymaltose)
- Carbonyl iron
- Sodium feredetate
- Combination of iron salts & Vit C, succinate, fructose
- Haemoglobin preparations

Oral iron preparations in market
- Around 200 oral preparations
- Different sources of Iron used
- More than one brand name for similar preparation by the same pharmaceutical company
Lot of variation in the combinations
  - Vitamins
  - Calcium
  - Other minerals
  - Haemoglobin
  - Liver extract
Marked variation in elemental iron
Consequences of variations
  - Ineffective prescriptions (persistent 10A)
  - Unwanted high cost of the therapy
Information about many other preparations not available in standard indexing resources
Insists that patient shows product information insertion

Case History
Female, 49 yrs (MA) presented on 21st April 06 for progressive weakness of 5 month duration. Clinical examination did not reveal any abnormality except pallor
Haemoglobin 3.3 gm%/dl, MCV 66.5 fl, MCH 15.8 pg, RDW 33.3, Serum iron 20 µg/ml, TIBC 434 µg/ml, TS 4.6%, Serum ferritin 8 ng/ml
No evidence of blood loss
Prescribed capsule fefol 1 BD. Haemoglobin on 5th May 06 : 3.6 gm/dl. On 5th June 06 : 4.2 gm/dl
? absorption problem and consider parenteral iron
Checked balance capsules. She was taking fefol Z capsules instead of Fefol and these capsules contained carbonyl iron
Changed to plain Fefol haemoglobin on 14th July 06 : 8.4 gm/dl and on 18th Sept 06 : 12.8 gm/dl

Oral iron preparations
Few examples of variations July 2006
  - Ferrium / Orofer
    - Ferrium capsules (iron 100 mg + 0.35 mg FA)
    - Ferrium C tablets (iron 100 mg + 1 mg FA)
    - Orofer capsules (iron 50 mg + 0.55 mg FA)
  - Globac
    - Globac capsules (ferrous fumarate 152 mg)
    - Globac capsules (formerly ferric ammonium citrate)
    - Globac PM (iron polymaltose)
  - Fefol
    - Fefol capsules (dried ferrous sulfate 150 mg)
    - Fefol Z (dried ferrous sulfate 150 mg + zinc)
• Fefoz Z (cabonyl iron 60 mg + zinc)
• Livogen
  • Capsules: ferrous fumarate (150 mg)
  • Liquid: ferrous gluconate (129.5 mg/5 ml)
• Dumasules
  • Capsules: ferrous fumarate (300 mg)
  • Dumasules Z: ferrous fumarate (100 mg)
• Mumfer
  • Capsules (2003): iron polymaltose
  • Capsules (2006): ferric ammoniumcitrate
• Iberol
  • Tablet: ferrous sulfate (525 mg)
  • Tonic: ferrous sulfate (131 mg/5 ml)
• Conviron TR
  • Dried ferrous sulfate (60 mg)

**Elemental iron content of iron slats**

<table>
<thead>
<tr>
<th>Iron salt</th>
<th>Elemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate (FeSO$_4$$ \cdot$ 7H$_2$O) 300 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ferrous sulfate dried 200 mg</td>
<td>65 mg</td>
</tr>
<tr>
<td>Ferrous fumarate 200 mg</td>
<td>65 mg</td>
</tr>
<tr>
<td>Ferrous gluconate 300 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous glycine sulfate 225 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Ferrous succinate 100 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous calcium citrate complex / cap</td>
<td>250 mg Fe + 85 Ca</td>
</tr>
<tr>
<td>Ferrous aminoate (probiotic cap)</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ferric ammonium citrate 100 mg</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

**Oral iron preparations**

**Desirable characteristics**

• Should have 150 mg elemental iron (at least 100 mg)
• Readily released in acidic and neutral pH (gastric and duodenal pH 5-6)*
• Prolonged release preparation less efficient
• Salt should be readily absorbable (Ferrous form)
• Infrequent side effects
• Should not have several therapeutic agents
• Small cost

*Maximum iron absorption in upper part of the duodenum

**Oral Iron Therapy - Important Points**

• One tablet of iron given without food is more effective than three tablets with meals
• Gastric discomfort subsides within a week with continued treatment without alteration of dose
• Diarrhea / constipation are not doses related
• Preparations marketed on basis of fewer side effects are invariably less absorbed
• Followup after 2 weeks of initiating treatment is very useful

**Poor Response to Oral Iron Therapy**

• Inappropriate choice and administration of iron preparation
• Noncompliance
• Insufficient duration of therapy
• Concurrent inhibitors of iron absorption
  • Antacids
  • \( H_2 \) blockers
  • Calcium salts
  • Phytates in food
  • Co-existent chronic inflammatory conditions
• On going blood loss
• Co-existence of vit. B\(_{12}\) & folic acid deficiency

**Iron Deficiency Anemia without GI Manifestations and GI Bleeding not responding to Oral Iron**

January 06 through December 06 \( n = 38 \), \( Age = 22 - 57 \) yrs, \( M = 22, F = 16 \) (unpublished personal data)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate iron preparation</td>
<td>28</td>
<td>72.5</td>
</tr>
<tr>
<td>( H. ) pylori infection</td>
<td>04</td>
<td>10.0</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>02</td>
<td>5.0</td>
</tr>
<tr>
<td>( H_2 ) receptor blockers</td>
<td>01</td>
<td>2.5</td>
</tr>
<tr>
<td>Angiodysplagia</td>
<td>01</td>
<td>2.5</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>00</td>
<td>0.0</td>
</tr>
<tr>
<td>No causes</td>
<td>05</td>
<td>7.5</td>
</tr>
</tbody>
</table>

**Case History**

• Female, 42 yrs (VS) presented on 26th May 06 for pain in abdomen and regurgitation after food. She complained of severe burning in mouth
• In 1988 low haemoglobin detected while in Australia
• Diagnosed as iron deficiency anemia, no loss of blood. Received 3 units of blood transfusion and was advised to take FeSO\(_4\) and life long omeprazole. Both of which she was taking for years

<table>
<thead>
<tr>
<th></th>
<th>1988</th>
<th>'88</th>
<th>'89</th>
<th>'94</th>
<th>5/06</th>
<th>4/06</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (gm/dl)</td>
<td>14</td>
<td>8.2</td>
<td>10.9</td>
<td>5.4</td>
<td>9.4</td>
<td>6.4</td>
</tr>
</tbody>
</table>

• On 26th May 06 - Haemoglobin 7.4 gm/dl, serum iron 72 \( \mu g/ml \), TIBC 486 \( \mu g/ml \), TS 14%, serum ferritin 8.5 ng/ml
• In view of persistent iron deficiency despite oral iron FeSO\(_4\) she was given injection Jectocos 1 ampoule at a time for 38 doses
• Haemoglobin after 4 weeks 10.6 gm/dl and Sept 06 14 gm/dl
• Burning in mouth has significantly decreased and rarely needs omeprazole
• Lesion : Choose parenteral iron in early stage if patient is not able to take oral iron preparation

**Iron Absorption on and off Omeprazole**

(Patient 1)

Serum iron levels after three tablets of ferrous sulphate 325 mg each. Note: Blunting of Iron absorption on omeprazole, but improved significantly after the cessation of omeprazole


**Diagnosis of Iron Deficiency**

**Diagnosis of Iron Deficiency of MCV / RDW**
Serum Iron Studies

- Estimation of serum iron
- Estimation of total iron binding capacity
- Calculation of transferrin saturation
- IDA - transferring saturation ≤ 15%

**Diagnosis of Iron deficiency anemia - use of serum ferritin**

55 studies culled from 1179 relevant citations. Mean area of receiver - operator characteristic curves in 2579 subjects (95% confidence limit)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td>0.95 ± 0.1</td>
</tr>
<tr>
<td>Erythrocyte zinc protoporphyrin</td>
<td>0.77</td>
</tr>
<tr>
<td>MCV</td>
<td>0.76</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>0.74</td>
</tr>
</tbody>
</table>


**Laboratory Methods for Iron Deficiency**

**Screening methods**

- Mean corpuscular volume and red cell distribution width (MCV and RDW)
- Transferrin saturation
- Reticulocyte haemoglobin content (CHr)
- Zinc protoporphyrin (ZPP)

**Definitive**

- Storage iron
  - Serum ferritin
  - Bone marrow haemosiderin
- Tissue Iron
  - Serum transferrin receptor (sTfR) (Soluble transferrin receptor)

**Reticulocyte Haemoglobin Content (CHr)**

- Reduction of CHr occur within few day of onset of IDE (half life of circulating reticulocytes is 1-2 days)
- Can be measured by only few models of cell counter i.e. (Bayer Advia, Sysmex)
- Low specificity
- False positive in
  - Macrocytosis
  - Thalassaemia


**Serum Transferrin Receptor (sTfR) Assay**

- Transferrin receptor - Glycoprotein on cell membrane
- “Gateway” for circulating transferrin to enter the cells
• Synthesis of TR is regulated by iron response protein
• Soluble form of TR found in the serum (Kohgo, 1986)
• Method: Enzyme linked immuno assay
• sTfR correlates with total mass of erythroid precursors and tissue iron deficiency
• sTfR increases in proportion to severity of iron deficiency
• Problem: Inter assay variation, therefore, not widely used
• Affected by - Bilirubin level, anticoagulant (EDTA vs heparin, serum vs plasma)

**Diagnosis of Iron Deficiency State**

• Isolated iron deficiency - simple to diagnose
  • Serum ferritin
  • Serum transferrin saturation
• Mild iron deficiency without anaemia
  • Missed by serum ferritin alone
  • Ratio of sTfR / serum ferritin*

* Cook JD et al - Detection of mild tissue iron deficiency *Blood*: 2000; 101; 3359 - 63.
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