Ironing Out the Details: A Review of Iron Deficiency Anemia and Safety Update for Iron Replacement Products

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Disclosure
• I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
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Objectives
• Compare and contrast different laboratory values used in the diagnosis of iron deficiency anemia
• Describe unique characteristics of different oral and parenteral iron replacement products
• Integrate safety information pertaining to administration of iron replacement products into patient care
Epidemiology

- Iron deficiency affects 2 billion people worldwide
  - Recent prevention efforts have recently decreased global rates of deficiency
  - Prevalence is now highest in Central and West Africa and South Asia
- Iron deficiency is the most common cause of anemia worldwide

Risk Factors

- Insufficient dietary intake
- Blood loss due to worm colonization
- Vegetarian diet
- Chronic blood loss
- Malabsorptive disorders (short bowel syndrome, inflammatory bowel disease)
- Reduced iron intake from prolonged breastfeeding and/or excessive cow’s milk intake
- Heavy menstrual bleeding in adolescent females
Definitions

• Anemia: Hemoglobin values that are more than 2 standard deviations below the mean
  – Men: Hgb < 13.4 g/dL, Women: Hgb < 12 g/dL
• Iron deficiency: reduction in iron stores
  – Reflected by a low ferritin
  – Anemia not necessarily present (Hgb still normal)
• Iron Deficiency Anemia = depleted iron stores result in low Hgb/Hct

Laboratory Parameters

- Complete Blood Count (CBC)
  - Hemoglobin (Hgb or Hb)
  - Hematocrit (Hct)
  - Red Blood Cell Count (RBC)
- Red Blood Cell Indices
  - Mean Corpuscular/Cell Volume (MCV)
    - MCH
    - MCHC
    - Red Cell Distribution Width (RDW)
- Iron Studies
  - Ferritin
  - Transferrin
  - Iron
  - Total Iron Binding Capacity (TIBC)
  - Transferrin Saturation (% Sat)

CBC

• Dependent on RBC mass and plasma volume
  – Values decrease when plasma volume increases (dilution)
  – Values increase when plasma volume decreases (hemoconcentration)
Red Blood Cell Count (RBC)

- The number of red corpuscles in a given amount of blood
- Normal Values
  - Adult Men: 4.5-5.9 x 10^6 cells/μL or 4.5-5.9 x 10^{12} cells/L
  - Adult Women: 4.1-5.1 x 10^6 cells/μL or 4.1-5.1 x 10^{12} cells/L

Hemoglobin (Hgb)

- A protein found in blood cells that carries oxygen to tissues
- Laboratory Value
  - The amount of the protein found in a given volume of whole blood (usually 100 mL)
  - Provides an indication of the oxygen transport capacity of the blood
- Normal Values
  - Men: 14-17.5 g/dL
  - Women: 12.3-15.3 g/dL

Hematocrit (Hct)

- The percentage volume of blood that is composed of erythrocytes
- Also known as the packed cell volume
- Generally three times the value of Hgb
- Normal Values
  - Men: 42-50%
  - Women: 36-45%
Mean Corpuscular/Cell Volume (MCV)

- Measure of the average red blood cell volume
- Calculation: \( MCV = \frac{Hct}{RBC} \)
- Determines the type of anemia
  - Macrocytic (MCV > 100 fL/cell)
    - Causes: Vitamin B12 deficiency, folate deficiency, increase in peripheral reticulocytes, cold agglutinins
  - Normocytic (MCV 80-100 fL/cell) *normal range*
  - Microcytic (MCV < 80 fL/cell)
    - Causes: Iron deficiency anemia, β-thalassemia

Mean Corpuscular/Cell Hemoglobin (MCH)

- Measure of the concentration of hemoglobin in a given volume of packed red blood cells
- Calculation: \( MCH = \frac{Hgb}{RBC} \)
- Normal range: 320-360 g/L
- Describes the color of the red blood cells
  - Low MCH = Hypochromic (pale)

Mean Cell Hemoglobin Concentration (MCHC)

- Calculation: \( MCHC = \frac{Hgb}{Hct} \)
- Normal Value: 33 g/dL
- Iron deficiency is the only anemia in which the MCHC is routinely low
  - Other disorders of hemoglobin synthesis will cause MCHC to be low
Red Cell Distribution Width (RDW)

- Measure of the variation of red blood cell width
- Coefficient of variation of the MCV
  - Calculation: \( \text{RDW} = \frac{\text{Standard deviation of MCV}}{\text{Mean value of MCV}} \times 100 \)
  - Normal range: 11-14%
- Helps determine if anemia is from a single or mixed cause
  - Elevated level = anisocytosis (variation in red cell size)

Serum Ferritin

- Iron-protein complex found in macrophages
  - Some found in serum
- Measure of iron stores in the body
- Normal range: >10-20 \( \mu \text{g/L} \)
- Acute phase reactant

Serum Transferrin and Iron

- Transferrin
  - Iron-protein complex responsible for iron transport
  - Reflects total iron binding capacity
  - Normal Range: 200-400 mg/dL
- Iron
  - Measures iron bound to transferrin
  - Normal range: 50-150 \( \mu \text{g/dL} \)
Total Iron Binding Capacity (TIBC)

- Measure of the iron binding capacity of transferrin
- Increased in IDA due to a compensatory increase in transferrin synthesis
- Normal Range: 250-410 μg/dL

Transferrin Saturation (% Sat)

- Calculation: % Saturation = \( \frac{\text{Serum Iron}}{\text{TIBC}} \)
- Iron deficient erythropoiesis exists if % Saturation is <15%
- Decreases in IDA because TIBC is increased

Is this Iron Deficiency Anemia?

- 42 year old female with crohn's disease, parenteral nutrition dependent, receives minimal oral intake
- CBC: RBC = 3.8 x 10⁶ cells/μL; Hgb: 9.4 g/dL; Hct: 31%
- Cell Indices: MCV=70 fl/cell; MCH: 237 g/L; MCHC=30 g/dL; RDW: 15%
- Iron Studies: Ferritin: 9 μg/L; Transferrin: 415 mg/dL; Iron: 40 μg/dL; TIBC: 440 μg/dL; % Sat: 9%
Iron Deficiency Anemia vs. Anemia of Chronic Inflammation

<table>
<thead>
<tr>
<th>Test</th>
<th>Iron Deficiency Anemia</th>
<th>Anemia of Chronic Inflammation</th>
<th>α- or β-Thalassemia Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>↓</td>
<td>↓</td>
<td>L (6-11)</td>
</tr>
<tr>
<td>Hct</td>
<td>↓</td>
<td>↓</td>
<td>L (22-31)</td>
</tr>
<tr>
<td>MCV</td>
<td>↑</td>
<td>↑</td>
<td>↑ (MA-11)</td>
</tr>
<tr>
<td>MCH</td>
<td>↑</td>
<td>↑</td>
<td>↑ (MA-11)</td>
</tr>
<tr>
<td>RRBC</td>
<td>↑</td>
<td>↑</td>
<td>↑ (MA-11)</td>
</tr>
<tr>
<td>Serum iron</td>
<td>↓</td>
<td>↑</td>
<td>↑ (MA-11)</td>
</tr>
<tr>
<td>TIBC</td>
<td>↑</td>
<td>↑</td>
<td>↑ (MA-11)</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>↓</td>
<td>↑</td>
<td>↑ (MA-11)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>↑</td>
<td>↑</td>
<td>↑ (MA-11)</td>
</tr>
<tr>
<td>Transferrin receptor</td>
<td>↑</td>
<td>↑</td>
<td>↑ (MA-11)</td>
</tr>
</tbody>
</table>

Oral Iron Replacement Therapies

Enteral Iron

- Absorbed from diet in the duodenum and proximal jejunum
  - Reduced to ferrous form by duodenal cytochrome b
  - Ferrous form of iron transported into the enterocyte by divalent metal transporter 1
  - Ferrous iron can then be stored as ferritin or is shunted to ferroportin, which converts it into ferric iron.
  - Ferric iron immediately binds to transferrin and is transported to the bone marrow for hemoglobin synthesis
Drug-Food Interactions With Iron

• Enhances iron absorption:
  – Vitamin C

• Decreases iron absorption:
  – Taking iron supplement with meat
    • Saturable enterocyte absorption
  – Calcium
  – Fiber
  – Tea/coffee

Oral Iron Therapies

<table>
<thead>
<tr>
<th>Iron Supplement</th>
<th>Elemental Iron Content</th>
<th>Iron Salt Content</th>
<th>% Elemental Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous Fumarate</td>
<td>106 mg</td>
<td>324 mg</td>
<td>33</td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>65 mg</td>
<td>325 mg</td>
<td>20</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>37.5 mg</td>
<td>324 mg</td>
<td>11.6</td>
</tr>
</tbody>
</table>

• Multiple products of various iron content exist
• These preparations are equally bioequivalent
• Recommended dose:
  – Adult: 100-200 mg/day in 2-3 divided doses
  – Pediatric: 3-6 mg/kg/day in 3 divided doses

Multivitamins With Iron

• Poly-vi-sol® with iron: 1 mL = 10 mg iron
• Flinstones™ with iron: 1 tablet = 18 mg iron
• One-a-Day® Women’s: 1 tablet =18 mg iron
• One-a-Day® Men’s: 1 tablet = none
• Centrum® Silver: 1 tablet = none
Common Adverse Effects

• Nausea
• Vomiting
• Stomach pain
• Constipation
• Darkening of stools
• Contact dermatitis

Intravenous Iron Replacement Therapies

Indications for Intravenous Iron
**Intravenous Iron**

- All products are colloids of spherical iron-carbohydrate nanoparticles
  - Core of each particle: iron-oxyhydroxide gel
  - A carbohydrate shell is required to stabilize the core, slow down the release of bioactive iron, and maintain a colloidal suspension
- Products differ in the size of the core and the type and density of the surrounding carbohydrate

**Mechanism of Action**

- When administered:
  - The iron carbohydrate complex is phagocytized by macrophages
  - Iron is released from the complex and then assimilated into ferritin or released into extracellular transferrin

**Intravenous Iron Options**

- **First Generation**
  - Iron Dextran (High Molecular Weight)
- **Second Generation**
  - Iron Dextran (Low Molecular Weight)
  - Sodium Ferric Gluconate
  - Iron Sucrose
- **Third Generation**
  - Ferrumoxytol
  - Ferric Carboxymaltose
### Comparison of IV Iron Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Carbohydrate</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Dextran*</td>
<td>Dextran polysaccharides</td>
<td>400,000</td>
</tr>
<tr>
<td>Low Molecular Weight Iron Dextran</td>
<td>Dextran polysaccharides</td>
<td>150,000-165,000</td>
</tr>
<tr>
<td>Sodium Ferric Gluconate</td>
<td>Gluconate</td>
<td>289,000-444,000</td>
</tr>
<tr>
<td>Iron Sucrose</td>
<td>Sucrose</td>
<td>34,000-60,000</td>
</tr>
<tr>
<td>Ferrumoxyl</td>
<td>Polyglucose sorbitol carboxymethyl ether</td>
<td>750,000</td>
</tr>
<tr>
<td>Ferric Carboxymaltose</td>
<td>Carboxymaltose</td>
<td>150,000</td>
</tr>
</tbody>
</table>

*High Molecular Weight Iron Dextran is now discontinued in the United States

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### Iron Dextran

- FDA Approved Indication: Iron deficiency anemia in which oral therapy is unsatisfactory or impossible
- FDA approved for ages 4 months or older
- Black Box warning for hypersensitivity reactions
  - Mandates a test dose be given

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### Black Box Warning

BOXED WARNING

WARNING: RISK FOR ANAPHYLACTIC-TYPE REACTIONS

Anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection.

- Have resuscitation equipment and personnel trained in the detection and treatment of anaphylactic-type reactions readily available during INFID administration.
- Administer a test INFID dose prior to the first therapeutic dose. If no signs or symptoms of anaphylactic-type reactions follow the test dose, administer the full therapeutic INFID dose.
- During all INFID administrations, observe for signs or symptoms of anaphylactic-type reactions. Fatal reactions have followed the test dose of iron dextran injection. Fatal reactions have also occurred in institutions where the test dose was not utilized.
- Use INFID only in patients in whom clinical and laboratory investigations have established an iron deficient state not amenable to oral iron therapy.
- Patients with a history of drug allergy or multiple drug allergies may be at increased risk of anaphylactic-type reactions to INFID.
Test Dose

Assesses tolerance of patient to the medication

- **Pediatrics:**
  - Infants <10 kg: 10 mg
  - Children 10-20 kg: 15 mg
  - Children >20 kg: 25 mg

- **Adults:** 25 mg x 1 dose

- Monitor for 1 hour after administration
  - If tolerated, can give remainder of doses after

- Have medications for reactions pre-ordered PRN
  - Diphenhydramine, hydrocortisone, epinephrine

- May cause false reassurance

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**Dosing: Iron Deficit Calculation**

- **Iron Deficit (mg) =**
  
  \[
  0.3 \times \text{weight in lbs} \times \left(100 - \frac{\text{Actual Hgb}}{\text{Goal Hgb}} \times 100\right)
  \]

- Goal Hgb = 14.8 g/dL
- If <15 kg, goal is adjusted to 12 g/dL

- **Iron Deficit (mg) =**
  
  \[
  50 \times (0.442 \times (\text{Goal Hgb} - \text{Actual Hgb}) \times \text{LBW} + (0.26 \times \text{LBW})
  \]

- LBW = lean body weight
- For patients weighing 5-15 kg, use actual body weight

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**Iron Dextran: Intramuscular Administration**

- **Z-track Technique**
  - IM injection into buttocks (rotate daily)
  
  - Dosing:
    - Infants <5 kg: 25 mg
    - Children 5-10 kg: 50 mg
    - Children >10 kg, Adolescents, and Adults: 100 mg
    - Maximum: 100 mg (2 mL) per dose
    - Continue repletion until iron deficit given

- Not recommended due to side effects (discomfort, tissue damage, skin discoloration)
Iron Dextran: Intravenous Administration
• Pediatric and Adult Dosing
  – Up to 100 mg maximum per dose until iron deficit completed
  – Administered no faster than 50 mg/min
  – Dilution not recommended for this dosing regimen
  
Iron Dextran: Total Dose Infusion
• After test dose/monitoring, the remainder of the iron deficit is given to the patient
• Total replacement dose can be diluted in 250-1000 mL of normal saline
  – Dilution in 5% dextrose can cause an increased incidence of pain and phlebitis
  – Infused over 4 to 6 hours (dependent on dose)
  
Sodium Ferric Gluconate
• FDA approved for patients with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy
• FDA approved for ages 6 and older
• No black box warning
• No test dose required
**Dosing and Administration: Sodium Ferric Gluconate**

- **Adult**
  - 125 mg elemental iron/dose x 8 doses (total: 1000 mg elemental iron)
  - Can be diluted in 100 mL of normal saline or can be given undiluted (maximum rate: 12.5 mg/min)
  - Infused slowly over 1 hour during dialysis

- **Pediatric**
  - 1.5 mg/kg elemental iron (maximum: 125 mg) x 8 doses
  - Dilute in 25 mL of normal saline (giving undiluted not recommended)
  - Infused slowly over 1 hour during dialysis

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**Iron Sucrose**

- FDA approved for patients with anemia and chronic kidney disease
- FDA approved for ages 2 and older
- No black box warning
- No test dose required

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**Adult Dosing: Iron Sucrose**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing</th>
<th>Infusion and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis (HD) Dependent CKD</td>
<td>100 mg x 10 doses during consecutive HD sessions</td>
<td>Give undiluted as slow intravenous injection over 2-5 minutes or dilute in no more than 100 mL of normal saline and give over at least 15 minutes</td>
</tr>
<tr>
<td>Non-Dialysis Dependent CKD</td>
<td>200 mg x 5 doses over 14 days</td>
<td>Give undiluted as slow intravenous injection over 2-5 minutes or dilute in no more than 100 mL of normal saline and give over at least 15 minutes</td>
</tr>
<tr>
<td>Peritoneal Dialysis Dependent CKD</td>
<td>Day 1 and 14: 300 Day 28: 400 mg</td>
<td>300 mg doses: Dilute in no more than 250 mL normal saline and give over 1.5 hours 400 mg dose: Dilute in no more than 250 mL of normal saline and give over 2.5 hours</td>
</tr>
</tbody>
</table>
**Pediatric Dosing: Iron Sucrose**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing</th>
<th>Dilution and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis (HD) Dependent Chronic Kidney Disease (CKD)</td>
<td>0.5 mg/kg (maximum dose: 100 mg) every 2 weeks for 12 weeks</td>
<td>Give undiluted as slow intravenous injection over 5 minutes or dilute in 25 mL of normal saline and give over at least 5-60 minutes</td>
</tr>
<tr>
<td>Non-Dialysis Dependent and Peritoneal Dialysis Dependent Chronic Kidney Disease</td>
<td>0.5 mg/kg (maximum dose: 100 mg) every 4 weeks for 12 weeks</td>
<td>Give undiluted as slow intravenous injection over 5 minutes or dilute in 25 mL of normal saline and give over at least 5-60 minutes</td>
</tr>
</tbody>
</table>

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**Ferumoxytol**

- FDA Approved Indication: treatment of iron deficiency anemia in adult patients with CKD
- FDA approved for adults only
- Black Box Warning
- Test dose not required

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**Dosing and Administration**

- **Adult**
  - 510 mg elemental iron x 1 dose, followed by 510 mg elemental iron x 1 dose 3 to 8 days later
  - Infuse in 50-200 mL of normal saline or 5% dextrose over at least 15 minutes

- **Pediatric**
  - 5.8-12 mg/kg elemental iron/dose
  - Given over 15-60 minutes
• Randomized, double blind, placebo controlled, multicenter, multinational, phase III trial
• Screening period of up to 2 weeks followed by a five week treatment period
  – Day 1 visit (dose 1 given), Week 1 visit (dose 2 given; 2-8 days post dose 1), then weekly through week 5
  – Patients stratified in a 3:1 ratio to ferumoxytol:placebo
  – Study dose: 510 mg elemental iron per dose

**Inclusion Criteria**

- >18 years old
- Iron Deficiency Anemia
  - Hgb <10 g/dL
  - % Sat <20%
  - History of unsatisfactory oral iron therapy or unable to use oral iron

**Exclusion Criteria**

- History of allergy to IV iron
- Hgb ≤ 7 g/dL
- Serum ferritin >600 mg/mL
- Known non-iron cause of anemia
- Active infection
- Hematologic malignancy
- Receiving dialysis or had a GFR <30 mL/min/1.73 m²

**Patients randomized:** 812 patients

**Intent-to-treat/safety population:** 808 patients
  – Ferumoxytol group: 608 patients
  – Placebo group: 200 patients

**No difference in baseline characteristics**
• Adverse effects of special interest: moderate to severe signs of hypotension or hypersensitivity associated with IV iron use

• Conclusions
  – IV ferumoxytol was effective in increasing hemoglobin levels by >2 mg/dL with two 510 mg doses
  – Authors concluded that the medication was well tolerated
    • 49.2% of patients that received ferumoxytol had a treatment related adverse event
    • Most were mild to moderate in intensity
    • 3.6% of patients that received ferumoxytol experienced moderate to severe hypotension or hypersensitivity
• Adverse effects of special interest: moderate to severe hypotension requiring medical intervention/hospitalization, acute decreases in systolic blood pressure from baseline >30% during the 60 minute observation period, symptomatic hypotension, systemic allergic reactions (anaphylaxis), and milder symptoms of hypersensitivity.

FDA Warning

• Adverse effects of special interest: moderate to severe hypotension requiring medical intervention/hospitalization, acute decreases in systolic blood pressure from baseline >30% during the 60 minute observation period, symptomatic hypotension, systemic allergic reactions (anaphylaxis), and milder symptoms of hypersensitivity.

Black Box Warning

WARNING: RISK FOR SERIOUS HYPERSensitivity/ANAPHylaxis REACTIONS
See full prescribing information for complete boxed warning.

Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving Feraheme. Initial symptoms may include hypotension, syncope, unresponsiveness, cardiac/cardiorespiratory arrest.

- Only administer Feraheme when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.
- Observe for signs or symptoms of hypersensitivity reactions during and for at least 30 minutes following Feraheme infusion including monitoring of blood pressure and pulse during and after Feraheme administration.
- Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated.

Adapted from www.fda.gov
Monitoring: Ferumoxytol

- Monitor for at least 30 minutes after infusion and until clinically stable
  - Pediatric patients monitored for 1 hour after infusion
- Hypersensitivity reactions have occurred in patients that previously tolerated the medication

New Uses for Ferumoxytol

- Takes advantage of properties of the drug:
  - Ultrasmall, superparamagnetic iron oxide agent
  - $T_1$ shortening effects
  - Long blood-pool residence time
  - Clearance through the reticuloendothelial system
  - Does not include gadolinium
- Uses:
  - Vascular and nodal metastasis contrast agent
  - Macrophage cell labeling (research)
- Most published studies are in adults, but it has been used safely in pediatrics (CMH will publish this summer)
Ferric Carboxymaltose

- FDA Approved Indications: Iron deficiency anemia in patients who do not tolerate oral iron; Anemia of Non-Dialysis Dependent CKD
- FDA approved for adults only
- No Black Box Warning
- Test dose not required

Dosing: Ferric Carboxymaltose

- Adult
  - Less than 50 kg: 15 mg/kg elemental iron on day 1; repeat dose 7 days later
    - Maximum: 1500 mg elemental iron per course
  - Greater than or equal to 50 kg: 750 mg on day 1; repeat dose 7 days later
    - Maximum: 1500 mg elemental iron per course

Administration: Ferrous Carboxymaltose

- IV Push
  - Give undiluted at ~100 mg/minute
- IV infusion
  - Dilute to ≥ 2 mg/mL over at least 15 minutes
**Monitoring: Ferric Carboxymaltose**

- Monitor for at least 30 minutes after infusion and until clinically stable

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Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial

- Randomized, open-label, active-controlled, multicenter, non-inferiority trial
- Patients allocated in 1:1 fashion to ferric carboxymaltose or iron sucrose
- Ferric carboxymaltose: 15 mg/kg elemental iron (maximum dose: 750 mg)
  - Given as an undiluted IV push (rate=100 mg/min) on days 0 and 7 (maximum total dose = 1500 mg)
- Iron sucrose: 200 mg elemental iron
  - Given as undiluted IV push over 2-5 minutes on Days 0, 7, and 14, with two additional doses given between days 7 and 14 (total dose = 1000 mg)

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Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial

- Eligibility Criteria
  - ≥ 18 years old
  - Hemoglobin value ≤11.5 g/dL
  - Screening visit ferritin <100 mg/mL or ferritin <300 ng/mL when transferrin saturation was ≤ 30%
  - Chronically impaired renal function, defined as:
    - GFR <60 mL/min/1.73 m² (MDRD) or
    - Two consecutive measurements of a GFR <60 mL/min/1.73 m² during the screening period and documented kidney damage
  - Stable erythropoiesis stimulating agent dose (if using)
Conclusions:

- Ferric carboxymaltose was non-inferior to iron sucrose
  
  • Authors concluded that ferric carboxymaltose was statistically superior to iron sucrose for increase in hemoglobin

- Clinical significance of 1.13 vs. 0.92 g/dL?
  
  • Ferric carboxymaltose allows more iron to be administered safely in fewer infusions and over a shorter period of time than iron sucrose
  
  – Total amount of iron administered different between study groups

  • Generally well tolerated
• Retrospective, single center, cohort study

• Patients with iron deficiency anemia who received ferric carboxymaltose between June 1, 2014 and June 10, 2015 were included
  – Patients without anemia who received ferric carboxymaltose were excluded

• Dosing: 15 mg/kg (maximum: 750 mg/dose)
  – >50 kg: 2 doses given at least 7 days apart
    (maximum total dose: 1500 mg)
  – <50 kg: decision to give 1 or 2 doses was left to the hematologist; if 2nd dose given, given 7 days apart

• Administered over 15 minutes
• 84% of patients had no adverse event
• 7 Children reported an adverse effect during or immediately after their infusions:

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>High</th>
<th>Moderate</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria</td>
<td>1/7</td>
<td>1/7</td>
<td>Resolved</td>
</tr>
<tr>
<td>Rash</td>
<td>1/7</td>
<td>1/7</td>
<td>Resolved</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1/7</td>
<td>1/7</td>
<td>Resolved</td>
</tr>
<tr>
<td>Arthralgia</td>
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<tr>
<td>Headache</td>
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<td>Resolved</td>
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<tr>
<td>Vasovagal syncope</td>
<td>1/7</td>
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<td>Resolved</td>
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<tr>
<td>Hypertension</td>
<td>1/7</td>
<td>1/7</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

Conclusion:
– Ferric carboxymaltose was effective in increasing hemoglobin in adult and pediatric patients
– Ferric carboxymaltose was generally well tolerated

Contraindications to Iron Replacement Therapy
• Bacterial infection
• History of hypersensitivity reactions to product
  – No/low cross sensitivity between products
• Recent blood transfusion
Common Adverse Effects

• Transient adverse effects: nausea, vomiting, pruritus, headache, flushing
• Usually resolve within 48 hours: arthralgia, myalgia, back and chest pain
• Rare but serious: Hypersensitivity
• IM administration: permanent dying of skin

Monitoring

• If infusion reaction occurs, can slow infusion rate or give supportive medications and monitor for improvement
• Hypersensitivity reactions
  – Monitor at least 30-60 minutes after infusion
• Iron overload
  – Monitor ferritin 1 week after dose and every three months

The Future

• Iron Isomaltoside
  – Not FDA approved (available in Europe)
  – Allows for total dose infusion
• Serum hepcidin levels
Ironing Out the Details: A Review of Iron Deficiency Anemia and Safety Update for Iron Replacement Products

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