New Aspects to Optimize Epoetin Treatment with Intravenous Iron Therapy in Hemodialysis Patients

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Educational Objectives

– Review pharmacology of IV iron
– Evaluate safety and efficacy of IV iron
– Examine new methods for IV iron dosing
Normal Erythropoiesis

**Bone Marrow**

- Stem Cell
- BFU-E
- CFU-E
- Pro-erythroblast & erythroblast

**Circulation**

- Reticulocytes
- RBCs

**Red Blood Cell Development: Time to Mature**

- Day 0
- Day 12
- Day 18
- Day 20
- Day 22
- Day 25

BFU-E: burst-forming units-erythroid; CFU-E: colony-forming units-erythroid; RBC: red blood cells

Iron Metabolism:
Before and After Advent of ESAs

Iron metabolism in pre-ESA era

- Blood transfusions used to manage anemia
- IV iron supplementation unnecessary; transfused blood contained adequate iron supply
- Transfusion-related issues
  - Increases infection risk
  - Allergic reactions
  - Adverse immunologic effects
  - Iron overload
    - Serum ferritin levels > 1000-2000 µg/L
    - Tissue deposition and cell damage
    - Increased risk of infection

Iron Metabolism:
Before and After Advent of ESAs

Iron metabolism in post-ESA era

- Transfusion-related issues avoided
- Iron directed to Hgb formation
- ESA stimulated erythropoiesis
  - Functional iron deficiency often occurs
- Oral iron cannot keep up with iron losses
- IV iron supplementation required

Iron Deficiency Anemia:
Average Annual Iron Losses

Up to 3 grams of iron may be lost annually in each chronic hemodialysis (HD) patient

- Repeated laboratory test: 0.5 grams
- Accidental losses during HD: 1 gram
- Blood retention in dialyzer and tubing: 1 gram
- Normal iron losses: 0.5 grams

REMEMBER:
You lose twice the iron with a Hgb of 12 gm/dl as with a Hgb of 6 gm/dl

Scanning EM of IV Iron

Iron-dextran
Iron-sucrose
Iron-gluconate

Kudasheva and Cowman, Polytechnic University, Brooklyn, NY
IV Iron
Iron Core and Carbohydrate Shell

iron oxyhydroxide core

carbohydrate shell
Order of Core Size & Particle Size:
Iron Dextran >> Iron Sucrose > Ferric Gluconate
Intravenous Iron

Free Iron

Labile Iron
RES Processing of IV Iron Sucrose

![Graph showing Fe\(^{59}\) Uptake over time after IV Iron Sucrose](graph.png)

Prompt RBC Utilization of Iron Sucrose Nearly Complete within 1 Month

Increased Hgb Corresponded to Reduction in Mean EPO Dose

Maintenance Iron Dosing

- Compared facility level data from 24 Fresenius dialysis facilities
  
  Group 1—100 mg every other week (n=16)
  Group 2—25 mg every week (n=8)

<table>
<thead>
<tr>
<th>Group</th>
<th>% pts with Tsat 20-50 (%)</th>
<th>Mean Tsat (%)</th>
<th>Mean Ferritin (ng/ml)</th>
<th>Mean Hgb (g/dl)</th>
<th>% Pts Hgb 10-12 g/dl</th>
<th>Epo units per Administration</th>
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<tbody>
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<td>1</td>
<td>90</td>
<td>30.4</td>
<td>674</td>
<td>11.6</td>
<td>62.5</td>
<td>6,412</td>
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<tr>
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<td>69</td>
<td>26.6</td>
<td>540</td>
<td>11.5</td>
<td>59.9</td>
<td>7,665</td>
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</tbody>
</table>

Iron Sucrose
North American Clinical Trial

- 665 Hemodialysis patient received iron sucrose
  - Replacement—100 mg each treatment x 10
  - Maintenance—100 mg weekly x 10
  - Repeated as necessary to achieve and maintain K/DOQI targets
- 8,583 doses of iron sucrose
- 239 patient years

Iron Sucrose
Adverse Events

- No serious drug-related adverse effects
- No hypersensitivity reactions
- 29 non-serious drug-related events
  - Taste disturbance most common
  - Transient
  - Not dose related

Iron sucrose North American Clinical Trial

Infection

<table>
<thead>
<tr>
<th></th>
<th>Hospitalization Rate</th>
<th>Death Rate</th>
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<tbody>
<tr>
<td>USRDS</td>
<td>400</td>
<td>30</td>
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<tr>
<td>NACT</td>
<td>200</td>
<td>10</td>
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</tbody>
</table>

P = 0.08

P < 0.001

Hypersensitivity Reactions to Intravenous Iron

• Retrospective Review of Adverse Events
  – FOI surveillance database (FDA)
  – Jan 1997-Sept 2002
  – Iron dextran, SFG, IS
  – Anaphylaxis, anaphylactoid rxn, urticaria, angioedema
  – Normalized to 100 mg dose equivalents

Hypersensitivity Reactions to Intravenous Iron

All-Cause Fatal Reactions to Intravenous Iron

DRIVE Study Design

Inclusion criteria

<11 g/dl,
   ferritin 500 to 1200 ng/ml
   TSAT <25%
   epoetin dosage >225 IU/kg per wk or >22,500 IU/wk

Participants (n  134) randomized to no iron (control) or to ferric gluconate 1,000 mg IV in eight doses

EPO was increased 25% at baseline

Comparisons made using ANCOVA

Effect Modification of Iron on EPO Response

• Retrospective data from 209 hemodialysis patients for 13 – 69 months
• Monthly measurements
  – Predialysis Hgb
  – Tsat
  – Serum albumin
  – Kt/V;
• Quarterly measurements
  – predialysis serum ferritin
  – intact parathyroid hormone
• Analyzed the dynamic relationship between hemoglobin and Epo dose

Effect Modification of Iron on EPO Response

Control Engineering Approach to Anemia Management

Hemoglobin Response to Model Predictive Control vs Algorithmic Anemia Management Protocol

Control Engineering Approach to Anemia Management

Conclusions

• Iron deficiency impedes erythropoiesis
  – EPO resistance
• Intravenous iron replacement is almost always needed in hemodialysis patients
• Iron replacement is safe and effective
• Iron maintenance therapy decreases EPO dose
• Giving iron in excess amounts does not improve EPO sensitivity
• Individualized anemia management requires simultaneous modeling of iron and EPO
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