Utility and Stability of a Generic Sodium Ferric Gluconate in Complex With Sucrose

Anemia occurs in the majority of patients receiving chronic hemodialysis; it is associated with deteriorated cardiac function, decreased cognition and mental acuity, fatigue, and an increased risk for mortality. Although the use of erythropoiesis-stimulating agents (ESAs), such as recombinant human erythropoietin or darbepoetin alfa, can increase red blood cell production in patients receiving chronic hemodialysis, these drugs have drawbacks, including high acquisition costs and cardiovascular complications. As a result, a primary goal in the management of patients receiving chronic hemodialysis is to alleviate anemia using the lowest possible dose of ESAs.

Patients on hemodialysis commonly experience iron loss from gastrointestinal bleeding, blood tests, and the dialysis itself. In fact, patients on hemodialysis may lose an estimated 2 to 4 g of iron per year. Because adequate iron stores are essential for achieving maximum benefit from ESAs, iron supplementation often is a critical strategy to improve outcomes in patients undergoing chronic hemodialysis.

Iron supplementation is used in people undergoing chronic hemodialysis to maintain a state of iron sufficiency such that ESAs can affect the hemoglobin response more appropriately,” said Rajiv Agarwal, MD, professor of medicine, Division of Nephrology, Indiana University School of Medicine in Indianapolis. “If ESAs were administered by themselves without iron supplementation, dialysis patients would ultimately not respond with an increase in hemoglobin very effectively.”

**Iron Supplementation In Hemodialysis Patients**

Oval iron supplements commonly are used in patients with iron-deficiency anemia. However, various studies have demonstrated that oral iron preparations are not effective for replenishing or sustaining iron stores in patients undergoing chronic hemodialysis. Parenteral iron supplements are much more effective for replenishing iron stores in these patients. In accordance with this data, a report from the Centers for Medicare & Medicaid Services found that approximately 70% of patients on hemodialysis were administered parenteral iron in 2005.

Parenteral iron supplementation can be classified into 2 different approaches. For some patients, an iron loading or repletion phase may be necessary. “Initially, patients may have depletion of the iron stores and total iron deficiency, as reflected by a low ferritin and a low transferrin saturation,” said Dr. Agarwal. “In these patients, you would replete their iron stores by administering a gram of iron in divided doses.” The other approach to iron supplementation is a maintenance phase. “Most dialysis patients require ongoing iron therapy as long as they are receiving [ESAs] so they don’t become resistant to their effect. Periodic low-dose iron therapy using about 30 mg per week should be sufficient, although this dose may vary depending on the degree of iron loss in the patient,” he explained.

One of the first available parenteral iron formulations was a dextran-containing iron. These parenteral agents are effective in relieving anemia in chronic hemodialysis patients. The major advantage to the dextran-containing iron is that they can be given as a large dose in a single setting, said Dr. Agarwal. “However, the major concern with the use of these agents is the potential for [sometimes fatal] anaphylaxis.” As a result, we do not use the dextran-containing iron at our institution.

In 1999, the first non–dextran-containing parenteral iron formulation, Ferrlecit®, was approved in the United States. Ferrlecit® is a branded preparation of sodium ferric gluconate in complex with sucrose (SFGC). Its efficacy is similar to that of iron dextran; however, the absence of the immunogenic dextran moiety means that SFGC has a better safety profile than iron dextran. “With the newer non–dextran-containing agents, there is less of a concern about anaphylaxis, and they don’t have the black box warning of anaphylaxis,” said Dr. Agarwal. In fact, studies have reported that SFGC may be safe for use in patients who are allergic to or intolerant of iron dextran. In its undiluted form, Ferrlecit® is administered as a slow IV injection (at a rate of up to 12.5 mg/min) because hypotension has been reported with rapid IV administration of iron. The most common side effects associated with Ferrlecit® include nausea, vomiting and/or diarrhea, injection site pain, hypotension, cramps, hypertension, dizziness, dyspnea, and chest pain.

As a result of these properties, SFGC is widely used in the United States and a study has shown that it is associated with favorable pharmacoeconomics. However, SFGC cannot deliver the large absolute dose of iron in a single infusion like dextran-containing iron formulations. Thus, SFGC requires multiple infusions over a specific period of time, especially during the loading phase of iron repletion.

**Nulecit®: A Generic Sodium Ferric Gluconate in Complex With Sucrose**

A generic version of SFGC, Nulecit®, recently was approved for the treatment of iron-deficiency anemia in adults and pediatric patients at least 6 years old on chronic hemodialysis receiving supplemental erythropoietin. Nulecit® is a sterile preparation of SFGC in 5-mL vials containing approximately 20% sucrose and 9 mg/mL of benzyl alcohol. Each dose has an elemental iron content of 62.5 mg (12.5 mg/mL). Nulecit® may be administered by slow IV injection with a syringe containing the undiluted product or by slow IV infusion from an infusion bag after dilution in 0.9% sodium chloride solution. The product is conveniently supplied in vial dose form. The iron content of 62.5 mg per vial allows continuous dosing in accordance with the National Kidney Foundation Clinical Practice Recommendations for IV iron (22 to 65 mg per week) and may optimize delivery and minimize waste. As with Ferrlecit®, the absence of the dextran moiety means that no test dose is required before Nulecit® infusion.

A comprehensive pharmacokinetic analysis of Nulecit® and Ferrlecit® demonstrated bioequivalence between the products. The study included 240 healthy volunteers.
Stability of Nulecit®

To ensure that patients receive an adequate dose of parenteral agents in solution—either in diluted or undiluted form—its short-term stability at room temperature (RT) and under refrigeration must be assessed. This data also influences the operations and workflow of the hospital, outpatient infusion center, dialysis center, and pharmacy. The stability of Nulecit® was investigated in a study by Baribeault. Samples of undiluted Nulecit® in 10-mL syringes or diluted in IV infusion bags containing 0.9% sodium chloride solution were stored at RT or under refrigerated conditions (2°C-8°C). Undiluted, RT samples were stored for up to 48 hours and diluted samples were stored for up to 24 hours. All refrigerated samples were stored for as many as 7 days. The parameters evaluated were iron concentration and the apparent molecular weight of SFGC. All tests were performed on 2 different lots of Nulecit®.

A subsequent analysis showed that iron concentrations were identical in both lots and no substantial variations occurred over time under different conditions of storage or dilution. The apparent molecular weight of SFGC across all samples varied from 306,114 to 354,012 Da, well within the range of 289,000 to 440,000 Da specified in the FDA-approved prescribing information. Based on these data, the author concluded that the iron content and apparent molecular weight were stable under all experimental conditions. Undiluted Nulecit® was stable for no less than 2 days at RT and no less than 7 days under refrigerated conditions; diluted Nulecit® in IV infusion bags containing 0.9% sodium chloride solution was stable for at least 1 day at RT and at least 7 days under refrigerated conditions (Tables 1 and 2).

Table 2. Stability of Nulecit® Under Refrigerated Conditions

<table>
<thead>
<tr>
<th>Sample</th>
<th>Elemental Iron (mg/mL)</th>
<th>Apparent Molecular Weight (Da)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot A</td>
<td>Lot B</td>
</tr>
<tr>
<td>Control</td>
<td>12.9</td>
<td>12.9</td>
</tr>
<tr>
<td>Syringe test (no dilution)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>14.0</td>
<td>13.9</td>
</tr>
<tr>
<td>24 h</td>
<td>14.0</td>
<td>13.9</td>
</tr>
<tr>
<td>72 h</td>
<td>12.9</td>
<td>12.9</td>
</tr>
<tr>
<td>7 d</td>
<td>12.4</td>
<td>13.0</td>
</tr>
<tr>
<td>Bag test (dilution to an approximate concentration of 0.625 mg/mL iron)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>0.620</td>
<td>0.620</td>
</tr>
<tr>
<td>3 d</td>
<td>0.614</td>
<td>0.607</td>
</tr>
<tr>
<td>7 d</td>
<td>0.633</td>
<td>0.612</td>
</tr>
<tr>
<td>Bag test (dilution to an approximate concentration of 1.25 mg/mL iron)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>1.17</td>
<td>1.15</td>
</tr>
<tr>
<td>3 d</td>
<td>1.17</td>
<td>1.16</td>
</tr>
<tr>
<td>7 d</td>
<td>1.18</td>
<td>1.18</td>
</tr>
</tbody>
</table>

Nulecit®, a generic, non–dextran-containing iron formulation, has shown therapeutic equivalence to Ferrlecit® and in a study was associated with favorable pharmacoeconomics. The short-term stability of Nulecit® has the potential to enhance pharmacy workflow, minimize waste, and ensure the effective delivery of iron to patients with anemia.

Financial Disclosure Statement

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References