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Iron Supplementation in Renal Anemia

Steven Fishbane

Iron-deficiency frequently develops in patients with chronic kidney disease who are treated with recombinant human erythropoietin (rHuEPO). It results in reduced effectiveness of anemia therapy; patients may fail to reach hemoglobin targets or may require excessively large doses of rHuEPO.[1,2] It has been recognized widely that iron management, monitoring for iron deficiency, and effective iron supplementation forms a core component of anemia therapy. This review discusses the physiology of iron balance, derangements in iron balance in chronic kidney disease (CKD), and the diagnosis and treatment of iron deficiency in patients treated with rHuEPO.
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Iron is required by all cells of the body for essential processes involving energy storage. In addition, its unique function in red blood cells allows hemoglobin to carry oxygen to the body's tissues and organs. Although iron is a vital element for life, it also has the capacity to cause harm via its great oxidative potential. As a result, the human body has highly developed systems for making iron available in a safe and highly regulated fashion.

There are 3 important compartments in which iron is found in the human body. Most iron, approximately 2,000 mg, is in the erythron, either in red blood cells or their precursors. Approximately one third of the body's iron (1,000 mg) is in storage tissues located in the bone marrow, spleen, and liver. A small amount of iron, approximately 3 mg, circulates in the bloodstream, primarily bound to the protein transferrin.

A very small amount of the body's iron (1 mg) is lost every day through the gastrointestinal tract. To maintain iron balance, the 1 mg lost needs to be replaced from dietary sources. The typical American diet contains 10 to 15 mg of available iron, a far greater quantity than typically needs to be absorbed.[3] It should be clear that even with sharp reductions in intake that there usually is sufficient dietary iron available. Therefore, reduced oral intake is an uncommon cause of iron deficiency, most iron deficiency occurs as a result of blood loss.

Winthrop-University Hospital, Mineola, NY.
Address reprint requests to Steven Fishbane, MD, 200 Old Country Rd, Suite 135, Mineola, NY 11501. E-mail: sfishbane@metrorenal.com

Iron Pathobiology in CKD

In CKD, deranged iron metabolism is understood best in hemodialysis patients. These patients become iron deficient primarily as a result of relentless ongoing blood loss[4] as a result of blood retention in the dialysis filter and lines, blood sampling for laboratory testing, and accidental blood loss from surgery and other sources.[5] Patients with blood loss often can compensate by increasing intestinal iron absorption. In fact, hemodialysis patients may have a relatively normal capacity for iron absorption.[6] However, the use of phosphate binders with meals probably reduces the ability to access dietary iron optimally.

A secondary change in iron balance occurs as a result of treatment with rHuEPO agents. During pharmacologic treatment large doses lead to a burst of erythropoiesis, probably faster than natural red cell production rates. The small circulating iron pool (3 mg) may be exhausted rapidly, and storage iron pools may not be able to release sufficient quantities of iron fast enough to keep up with the accelerated erythropoiesis. As a result, functional iron deficiency often occurs. In this state, despite adequate bone-marrow iron stores, iron-deficient erythropoiesis may occur.[7] Iron indices may reflect adequate storage iron levels (normal serum ferritin) but with reduced circulating iron levels (transferrin saturation).

Inflammation often is present in patients on hemodialysis, with a significant impact on iron metabolism.[8] During inflammatory states, hepcidin, a key regulator of iron metabolism produced by the liver, drives iron out of circulation and into storage tissues.[9] To the extent that inflammation is caused by infection, then this is an adaptive response, temporarily depriving bacteria of iron needed for growth. In

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hemodialysis patients, in whom occult inflammation is a common problem and often is not caused by infection, iron availability may be impaired severely. Clinical recognition may be difficult; patients may have high levels of serum ferritin yet may respond poorly to rHuEPO treatment. C-reactive protein levels and other serum markers for inflammation may be increased.

Diagnosis of Iron Deficiency in Hemodialysis Patients

Serum ferritin and transferrin saturation are the most frequently used tests for the detection of iron deficiency in CKD. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines for the treatment of anemia recommend target levels of serum ferritin of 100 ng/mL and transferrin saturation of 20%.[10] Many published studies, however, have indicated that the serum ferritin target of 100 ng/mL may underestimate the frequency and severity of iron deficiency in hemodialysis patients.[11-14] It appears that less than half of hemodialysis patients who are iron deficient are identified by this serum ferritin level.[11,12] In addition, 2 randomized controlled trials have found greater efficacy of iron treatment at higher levels of serum ferritin. Besarab et al[15] randomized 42 hemodialysis patients to intravenous iron treatment with target transferrin saturation of 20% to 30% or 30% to 50%. The subjects in the low transferrin saturation group achieved a mean serum ferritin level of 297 ng/mL, those in the high group had a mean serum ferritin level of 730 ng/mL. The higher ferritin level was associated with greater treatment efficacy, with a mean 40% reduction in rHuEPO dose. DeVita et al[16] randomized 36 hemodialysis patients to intravenous iron treatment targeted to serum ferritin levels of 200 or 400 ng/mL (levels of 299 ng/mL and 469 ng/mL were achieved). In the higher serum ferritin group the rHuEPO dose requirements were decreased by 28%. Taken together, these studies suggest that a higher target level of serum ferritin than 100 ng/mL might be justified for hemodialysis patients.

Iron Treatment in Patients With Nondialysis-Dependent CKD

The approach to iron supplementation is best considered when classified based on the stage of kidney disease. For patients with nondialysis-dependent CKD, iron supplementation often is used as an adjuvant to rHuEPO therapy. The patient with CKD does not experience the ongoing blood loss that hemodialysis patients do, so severe iron deficiency probably is rare. Unfortunately, there is insufficient published evidence to define clearly either the frequency or consequences of iron deficiency in CKD. Factors that might predispose to iron deficiency in this population include occult gastrointestinal bleeding, repeated blood draws for laboratory testing, interference with dietary iron absorption by phosphate binders, and increased iron demand induced by rHuEPO treatment.

The simplest and least expensive form of iron supplementation for patients with CKD is by the oral route. At the time of this writing, a 3-month supply of ferrous sulfate had a retail cost of approximately $8 (United States, www.drugstore.com). There are several problems with oral iron supplementation. The most important is the frequent occurrence of gastrointestinal side effects such as dyspepsia and constipation.[17] The etiology of gastrointestinal irritation may be related to induction of reactive oxygen species in the intestinal mucosa.[18] The development of side effects probably limits compliance with oral iron supplements. To reduce symptoms and to improve compliance, patients may be instructed to take the pills with meals. This will reduce symptoms but will limit the drugs' effectiveness. Another strategy for limiting side effects is the use of enteric-coated formulations of oral iron. Because iron is absorbed very proximally in the gastrointestinal tract, enteric-coated formulations may fail to disintegrate and release iron early enough, potentially bypassing the absorbing segments. A second problem with oral iron supplementation is the contribution to polypharmacy in patients with CKD. Patients take a large number of oral medications, and iron supplements taken 3 times a day between meals may worsen the overall burden.

The efficacy of oral iron in CKD has not been studied adequately. Evidence for efficacy ideally would come from a randomized controlled trial comparing oral iron with placebo (or less optimally with no iron treatment). Surprisingly, such a study has not been performed. As a result there is no evidentiary basis for a recommendation on the use of oral iron supplements in patients treated with rHuEPO. It is my opinion, however, that in CKD patients whose iron test results indicate iron deficiency that oral iron treatment should be initiated. Ferrous sulfate, 325 mg 3 times a day between meals, supplies 195 mg of elemental iron per day. Other iron salts and carbohydrate complexes are available, although none has been shown to have greater efficacy or tolerability. There is emerging evidence that heme iron may be better tolerated than iron salts.[17] Heme iron polypeptide is available as an over-the-counter food supplement with 12 mg of elemental iron per tablet. Nissenson et al[19] compared heme iron polypeptide with intravenous iron treatment in hemodialysis patients, finding heme iron polypeptide to have reasonable efficacy and tolerability.

In some patients with CKD oral iron supplementation may not treat iron deficiency sufficiently, in which case intravenous iron therapy should be considered. It is important first to address the patient's compliance with oral iron, and to explore whether side effects or difficulty paying for the agents have been an issue. In addition, the possibility of occult gastrointestinal or other blood loss should be considered. Resistant iron deficiency always should raise concern for an underlying intestinal malignancy.

Intravenous iron is a useful alternative form of iron supplementation. However, it requires establishment of intravenous access, which may be inconvenient for many patients. In addition, there are potential safety concerns regarding renal tubular toxicity[20] and damage to blood vessels that eventually may be needed for vascular access. Among patients on

hemodialysis, as discussed later, intravenous iron therapy has great efficacy, improving the efficiency of rHuEPO treatment. In CKD, the efficacy of intravenous iron is not well established. Aggarwal et al[21] studied 40 CKD patients treated with rHuEPO. Patients were randomized to either intravenous or oral iron treatment. At study conclusion, the mean hemoglobin level was 1.1 g/dL higher in the intravenous iron group. Similarly, Silverberg et al[22] studied 90 CKD patients treated with intravenous iron with or without accompanying rHuEPO. Five weekly intravenous doses of 200 mg of iron sucrose were found to improve the response to rHuEPO significantly. In contrast, Stoves et al[23] studied 45 CKD patients treated with rHuEPO who were randomized to treatment with oral or intravenous iron. No significant difference in efficacy between the 2 iron treatments was noted. Charytan et al[24] randomized 96 CKD patients to treatment with intravenous iron sucrose or oral iron supplementation. There was no significant difference in mean hemoglobin level between the 2 groups at study conclusion. Finally, Van Wyck et al[25] randomized 161 CKD patients to treatment with intravenous iron sucrose or oral ferrous sulfate, and found improved efficacy with intravenous iron. An increase in hemoglobin level of 1 g/dL occurred in 44% of patients treated with intravenous iron compared with 28% treated with oral iron. Taken together, these studies yield mixed information regarding the efficacy of intravenous iron in patients with CKD. The efficacy appears to be superior to oral iron, but the effect size is quite modest.

When intravenous iron is required for patients with CKD, this may be administered as a slow infusion or a bolus injection. Most experience has accrued using a slow infusion, and the relative safety of giving iron as a 'push' injection is not clear at the present time. Doses of up to 250 mg of iron sucrose or sodium ferric gluconate can be administered over 2 hours. Mild hypotensive reactions may occur, so the patient should be closely observed during the infusion. The need to establish vascular access and the long duration of infusion may be excessively inconvenient for many patients. Recently, Macdougall et al[26] reported on 2 minute push injections of iron sucrose in patients with CKD. The administrations were generally well tolerated with mild side effects, and this had the obvious benefit of increased convenience, but 7 patients experienced hypotensive reactions. Furthermore, intravenous iron injection results in a transient increase in oxidative stress. Most injections are slower than the 2 minutes used in this study, and are diluted either with saline or by injection into high flow hemodialysis accesses. Rapid injection of iron into native veins with slow blood flow might theoretically create excess risk for oxidative tissue injury. This is particularly important as these veins may ultimately be required for creating AV fistulae. There is therefore a need for randomized controlled studies to investigate the relative safety of administering IV iron as a bolus injection versus a slow infusion, with regard to both the incidence of hypotensive reactions and the risk of oxidative stress. Iron dextran infusions allow the possibility of larger dose infusions, but the risk for anaphylaxis limits the use of this agent.

Iron Treatment for Hemodialysis Patients

Among hemodialysis patients, iron monitoring and treatment take on greater importance. Repeated blood loss related to the dialysis procedure results in iron deficiency in a large number of patients.[5] The effectiveness of anemia therapy with rHuEPO may be hindered, resulting in patients whose hemoglobin levels do not increase to the target level. Because hemoglobin levels less than the National Kidney Foundation Kidney Disease Outcomes Quality Initiative target of 11 to 12 g/dL are associated with suboptimal outcomes,[27] iron support is a key component of care.

Oral iron treatment generally is not effective for patients on hemodialysis. Three published studies have randomized patients to treatment with oral iron compared with either no iron or placebo. Markowitz et al[28] randomized 49 hemodialysis patients to double-blinded treatment with oral iron polysaccharide or placebo. The primary finding was that oral iron had no significant efficacy compared with placebo. Fudin et al[29] randomized 39 hemodialysis patients to treatment with oral iron, no iron, or intravenous sodium ferric gluconate. The intravenous iron was found to be significantly more effective than oral iron and there was no significant difference between oral and no iron treatment. Finally, Macdougall et al[30] randomized 37 patients to treatment with intravenous, oral, or no iron and found results very similar to those of Fudin et al.[29] Intravenous iron was more effective than oral iron, and there was no significant difference between oral and no iron treatment. Taken together, these studies indicate that oral iron does not have clearly defined efficacy for treatment of hemodialysis patients.

Intravenous iron therapy is highly effective as an adjuvant to rHuEPO in hemodialysis patients. A large body of published studies supports the value of treatment for improving hemoglobin levels and/or reducing the required rHuEPO dose.[29-38] There are 2 general strategies used for iron treatment in hemodialysis patients. The first is repletive: when iron deficiency is detected a large repletive course of intravenous iron is administered. Typically, 1,000 mg of intravenous iron is given over 8 to 10 hemodialysis treatments. This approach is effective, although many patients will have a recurrence of iron deficiency within several months.[31] Alternatively, iron deficiency may be prevented with regular repeated doses of intravenous iron. Typically, 25 to 100 mg of iron is given on a weekly basis. This treatment strategy may be more effective for preventing a recurrence of iron deficiency, but it also occasionally may result in progressive increases in serum ferritin levels.[15,38] There have been very few studies directly comparing the 2 approaches to treatment; either may be valuable in specific clinical situations.

Iron Treatment for Peritoneal Dialysis Patients

For patients on peritoneal dialysis, many principles of iron treatment mirror those discussed earlier for CKD. These pa-

tients do not experience the persistent blood loss of hemodialysis patients and, as a result, iron deficiency occurs less frequently. As was the case for patients with CKD, neither iron diagnosis nor treatment with oral iron has been well studied in this population. It would seem reasonable to treat with oral iron when a patient's serum ferritin level is less than 100 ng/mL or transferrin saturation is less than 20%. Intravenous iron should be reserved for patients who remain iron deficient after oral iron supplementation, and who fail to increase hemoglobin levels into the target range. There are very few randomized trials that have evaluated intravenous iron in peritoneal dialysis patients. Among nonrandomized trials, 2 had a reasonable design, showing improved efficacy of intravenous compared with oral iron.[39,40] In 1 cross-over study, Johnson et al[40] found that oral iron, although not as effective as intravenous iron treatment, had reasonable efficacy by itself. When intravenous iron is needed, an infusion of 100 to 250 mg of sodium ferric gluconate or iron sucrose may be administered over 2 hours.

Iron Treatment Safety

The major risk of intravenous iron treatment is that of anaphylactoid reactions. The terminology implies an immune or mechanical mast cell–mediated process. It is not clear, however, that these reactions truly represent this pathophysiology. It may be more correct to say that reactions have the phenotypic appearance of anaphylaxis (hence the term *anaphylactoid*). Typical reactions involve hypotension, dyspnea, back pain, flushing, and anxiety.[41] The syndrome is defined best with iron dextran. With this agent, hypotension may develop very rapidly, at times while the intravenous injection is still in progress. When dextrans first were used as volume expanders, anaphylaxis was an occasional catastrophic complication. With iron dextran, such reactions have been observed and reported anecdotally. It has been estimated that severe reactions occur in approximately 0.7% of patients treated with iron dextran.[41] With sodium ferric gluconate and iron sucrose similar reactions may occur.[35,42] It is likely that reactions are less frequent and of lesser severity with these agents. The current literature is not developed to the point at which it is possible to define rigorously the relative rate of reactions with the different agents. There have been no well-designed, adequately powered comparative studies. Most published studies represent retrospective analyses of charts or databases. It is likely that either approach grossly is inadequate for the purpose. There has been only 1 study in which a reasonably sized sample of patients was observed directly after iron injection for the occurrence of reactions. Michael et al[43] studied 2,503 hemodialysis patients given sodium ferric gluconate or placebo in a blinded fashion by intravenous push. There was only 1 severe reaction observed with sodium ferric gluconate (0.04% of patients treated, not statistically different than the rate with placebo), the patient experienced hypotension and shortness of breath. The event remitted after 20 minutes, and the patient was able to finish dialysis and was not hospitalized. This is in stark contrast to the occasional catastrophic reaction with iron dextran, in which hospitalization and death may occur.[44] It is likely that both nondextran irons, sodium ferric gluconate, and iron sucrose carry a lower risk for severe reactions than iron dextran.

Another safety concern with intravenous iron treatment relates to risk for infection. Iron is an important growth factor for most living species, including infectious microorganisms. In animal studies iron administration has been found to promote infection[45,46] because (1) infections are a frequent challenge for hemodialysis patients, (2) iron is a vital growth factor for bacteria, and (3) hemodialysis patients often are treated with intravenous iron; it is plausible that there could be a relationship between intravenous iron treatment and risk for infection. In fact, several studies have found a relationship between higher serum ferritin levels (particularly $>$ 500 ng/mL) and risk for infection.[47-49] It is particularly difficult to determine whether this association represents causality because of ferritin's dual nature. Serum ferritin is an indicator of iron stores, but also a potent acute-phase reactant, with levels sharply increased by inflammation or infection. This duality of function confounds the relationship and weakens the strength of evidence of observational studies. Of note, a large, multicenter, prospective, European study did not find any relationship between serum ferritin level or iron treatment and risk for infection.[50] Despite the absence of definitive data, it would seem reasonable to avoid intravenous iron treatment in the setting of acute infection.

Another safety concern with intravenous iron treatment is the potential to induce oxidative tissue injury. Iron in certain conditions may cause oxidative changes in biomolecules such as DNA, proteins, or lipids.[51] Oxidative damage should occur only with direct contact between iron and tissues, not when iron is bound safely in complexes such as ferritin, transferrin, and hemosiderin. In the context of iron treatment, oxidative damage could occur if (1) iron overload were to develop in storage tissues, overwhelming the ability of storage complexes such as ferritin and hemosiderin to bind the iron safely, or (2) intravenous iron complexes directly released iron into the vascular space resulting in oxidative injury to blood vessels or other tissues. When intravenous iron treatment follows guidelines, iron overload should not occur. In contrast, direct iron release from intravenous iron drugs probably does occur. Rooyakkers et al[52] injected intravenous iron sucrose into normal volunteers and found free iron (not bound to the iron drug) in circulation, with a significant increase in oxidative stress. Zager et al[53] performed in vitro studies, finding that iron dextran, oligosaccharide, gluconate, and sucrose all led to some degree of lipid peroxidation. Recently, Leehey et al[54] administered sodium ferric gluconate to patients with CKD and found evidence of increased oxidative stress. Taken together, these and other studies indicate that there probably is some release of free iron into the circulation after injection of intravenous iron drugs, and that some degree of oxidative stress occurs. What is unclear is whether the oxidative stress leads to any harmful effects, either tissue injury or suboptimal outcomes. Transient, brief exposure to reactive oxygen compounds is very much a part of daily life, resulting from a large variety of environmental

exposures and endogenous metabolism. The body's antioxidant systems are designed to buffer the impact of oxidative stress. How oxidative exposure with intravenous iron treatment relates quantitatively and kinetically to other daily oxidative challenges is completely unclear. The subject, however, is highly relevant and potentially important; further research in this area is needed greatly.

Conclusions

Iron management is an important component of the overall care of patients with kidney disease who are treated with rHuEPO. Monitoring iron status and the diagnosis of iron deficiency result in the opportunity to treat patients effectively with supplemental iron. Iron treatment varies with the stage of kidney disease. In nondialysis-dependent CKD, oral iron may suffice; for patients on hemodialysis intravenous iron often is necessary. The effect of successful iron treatment is to improve the response to rHuEPO, allowing patients to reach target, healthy levels of hemoglobin.

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