Making Sense: A Scientific Approach to Intravenous Iron Therapy

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More than 100 yr have passed since parenteral iron was first given to humans (1). Fifty yr ago, carbohydrate iron was first coupled to iron oxide (2), reducing the fierce toxicity of ferric iron and introducing the era of parenteral therapy with carbohydrate-iron agents (3,4). This is sufficient time to consider what we have learned about the risks and benefits of intravenous (IV) iron therapy; to review what we know and what we don’t; and, most important, to develop a comprehensive, unifying view that makes sense of the chemistry, biology, and pharmacology of IV iron agents.

Although treatment of iron deficiency certainly is not confined to patients with kidney disease, the majority of published evidence on IV iron therapy resides in the nephrology literature. Anemia is common among all patients with chronic kidney disease, expected among those with advanced kidney disease, and nearly universal among those who undergo dialysis. Evidence of iron deficiency is currently quite common in patients with chronic kidney disease–associated anemia (5). However, before treatment with erythropoietin receptor agonists (ERA; including epoetin α, epoetin β, and darbeopetin α), it was iron excess, not deficiency, that afflicted most dialysis patients. Because anemia was severe, transfusion dependence was common, and transfusional hemosiderosis resulted.

ERA therapy ended transfusion dependence, unmasked iron loss as the dominant feature of iron balance in hemodialysis patients, converted iron overload to iron deficiency as the prevailing disorder, highlighted the failure of oral iron supplementation to sustain iron sufficiency, and thereby thrust IV iron agents to the forefront of iron replacement. Two additional developments have heightened IV iron use in dialysis patients. The first is evidence that a maintenance IV iron schedule designed to prevent iron deficiency is more effective than a periodic treatment schedule in achieving target hemoglobin and minimizing doses of ERA therapy. The second is acceptance and implementation of anemia management guidelines, including those of the National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) and European Best Practice Guidelines (EBPG). Publication of the first K/DOQI anemia guidelines in 1997 (6) and the EBPG anemia guidelines in 1999 (7) has been followed by gradual adoption of iron maintenance protocols. IV iron use in the United States has increased every year since 1996. By 2002, the proportion of patients who received IV iron within a single quarter approached 65%, and the average annual IV iron dose for all hemodialysis patients exceeded 2300 mg (8).

Increasing use of IV iron has prompted concerns for the potential hazards of iron therapy and the risks of iron overload and has stimulated a new and welcome wave of inquiry into iron safety. From in vitro studies to epidemiologic examination of large dialysis databases, evidence has accumulated rapidly. At the same time, new techniques to examine the structure and chemistry of iron carbohydrate compounds have helped to resolve decades-old controversies about how, for good or for bad, IV iron agents deliver biologically active iron.

A coherent, unifying view of IV iron agents, based soundly on an understanding of structure and chemistry, to encompass in vitro findings, explain in vivo observations, evaluate risks and benefits, and compare existing IV iron agents is urgently needed. During Renal Week in San Diego, California, in November 2003, Bo Danielson, George Aronoff, and David Van Wyck outlined one such view at a symposium sponsored and organized by the American Society of Nephrology. The current review arises from that collaboration. The groundbreaking work of Mary Cowman and Dina Kudasheva (9,10) on carbohydrate-iron structure and chemistry plays a central role in formulating our review. The findings of these two colloid chemists make possible a remarkable synthesis of the chemistry, biology, and clinical use of IV iron agents.

Our conclusions are reassuring. No IV iron compounds generate detectable free iron. All IV iron agents release biologically available or labile iron. The rate of labile iron release in each agent is inversely related to the size of its iron core. The clinical consequences of labile iron release have little significance at low iron doses but limit the maximum tolerated single dose and rate of infusion of each IV iron agent. All evidence suggests that, in regard to iron release, IV iron use within current guidelines is safe and that K/DOQI limits for iron supplementation (11,12) should continue to be observed.

References