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Safety issues with iron sucrose

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SAFETY ISSUES WITH IRON SUCROSE

To the Editor:

Recently, Yee and Besarab[1] published an in-depth review article on iron sucrose that I believe may have understated evolving data relating to safety concerns with the drug.

When administered intravenously, iron treatment has the potential to cause the circulation of free iron, with a variety of adverse consequences, including tissue oxidation and increased risk for infection. Generally, after intravenous dosing, iron drugs are taken up by cells in the reticuloendothelial system prior to release of iron to transferrin in the circulation. However, iron sucrose appears to release iron into the circulation immediately after dosing. Danielson et al[2] found that peak serum iron levels occurred in only 10 minutes, with direct transfer of iron to transferrin. This creates the potential to "overwhelm" transferrin, leading to free iron in plasma. In hemodialysis patients treated with iron sucrose (100 mg), Parkinnen et al[3] found serum iron levels rose almost immediately, leading to free iron in plasma in 50% of patients. Serum from these patients readily promoted the growth of staphylococcus epidermidis in vitro. Adding exogenous transferrin to the patient's plasma halted the bacterial growth, demonstrating that free iron was the culprit causing the bacterial growth.

Kooistra et al[4] studied iron sucrose (100 mg) in 10 stable hemodialysis patients. Serum iron was found to increase approximately 20-fold and transferrin saturation increased to over 400%, indicating full saturation with washover of free iron into the circulation. Indeed, by high-performance liquid chromatography (HPLC), they found a significant increase in nontransferrin bound iron. Rooyakkers et al[5] administered 100 mg iron sucrose intravenously to normal volunteers and found a 4-fold increase in nontransferrin bound iron in plasma, a 53% to 70% increase in superoxide generation, and a transient significant reduction in flow-mediated vasodilatation.

Zager et al[6] found that all intravenous iron drugs resulted in evidence of oxidation. However, it was found that iron sucrose led to profound cellular toxicity, leading to a nearly 90% decrease in cell viability. The authors believed that elucidation of reactive oxidation species with mitochondrial blockade and ATP depletion were the cause.

Tovbin et al[7] studied iron sucrose in 19 hemodialysis patients, finding a 37% increase in advanced oxidation protein products (AOPP). Drueke et al[8] studied 79 hemodialysis patients and found significant evidence for oxidative stress and acceleration of atherosclerosis in proportion to the amount of iron sucrose administered over a 12-month period. Triolo et al[9] compared iron sucrose to ferric gluconate in 61 hemodialysis patients, finding that the rate of infections in the iron sucrose treated group was 1 in 10 patient-months compared to only 1 in 17 patient-months in patients treated with ferric gluconate. They suggested that free iron release by iron sucrose may explain the findings.

Taken together, these and other data suggest that (1) iron sucrose releases iron too rapidly, (2) the rapid iron release overwhelms transferrin resulting in free iron in plasma, and (3) the free iron results in oxidative effects and increased bacterial growth seen in vitro and in vivo. The extent to which these adverse consequences of iron sucrose treatment may apply to other intravenous iron drugs is unclear, but further research is clearly indicated.

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In Reply:

Relevant to our review, "Iron sucrose: the oldest therapy becomes new,"[1] Fishbane contends that iron sucrose (IS) transfers iron directly to transferrin, promulgating oxdative tissue damage[2] and bacterial proliferation.[3] These concerns deserve merit, but may be equally applicable to other parenteral irons, iron dextran (ID), and iron gluconate (IG). Thus, the fundamental issue is not whether these potential iron-related hazards are IS-specific, but whether the quality of the present data surrounding these issues is sufficient to contend the above for any of the therapeutic irons.

Transferrin "oversaturation" was initially described for IG[4] and stemmed from iron release in plasma from its drug-ligand,[5] thereby rendering transferrin saturation >100% as it became the sum of transferrin-bound and ligand-bound iron. This oversaturation is also a function of drug half-life.[5] Calculations of oversaturation in the studies of Danielson et al[5] and Kooistra et al[6] are flawed as both used the same recently discredited iron assay that was also used to determine an IS half-life of 6 hours.[5] Despite that ID shields iron to the greatest extent among the irons, it, along with IS and IG, directly donates iron to transferrin in vitro.[7-9] However, the clinical hazard of this donation is presently unquantified. Lastly, transferrin oversaturation might actually be attributable to a small proportion of free or loosely bound iron that is present in parenteral iron.

Nontransferrin bound iron (NTBI) is present in normal serum, hemachromatosis, and the thalessemias and increases after parenteral iron administration.[9] NTBI clearly increases following IS delivery in vitro or in vivo, but no "head-to-head" comparative studies among the different preparations exist that use comparable assay systems.[8,11] More importantly, do transferrin-independent iron transport mechanisms clear NTBI after exposure to parenteral irons, in contradistinction to hemochromatosis where transferrin binding is continually superseded?

The potential harm of IS as postulated by Parkinnen et al[3] and Zager et al[2] has not been borne out. The bacteriologic studies do not unequivocally prove that *S epidermidis* proliferation resulted from free iron as bacteria have evolved unique systems of iron uptake (siderophores) through which NTBI may be utilized to enhance growth. Moreover, bacterial growth suppression by exogenous transferrin does not provide clearcut evidence that free iron was present, because transferrin's iron association constant is orders of magnitude greater than any other plasma chelator or transporter. Similarly, iron toxicity in cell culture[3] cannot be directly translated to the in vivo circumstance. The iron preparation concentrations of these in vitro studies exceeds the conventionally achieved in vivo concentrations of IS and IG. The lowest concentration that was studied is potentially achievable only after a large-dose ID infusion. With regard to the oxidative effects on proteins and lipids by IS, we believe that no definitive or extrapolatable conclusions regarding the relative toxicities of the parenteral irons should be ascertained until direct comparison trials between IG and ID appear. However, we agree, along with others, that parenteral iron should be withheld from patients with an active infection or inflammatory process.

Lastly, there is demonstrated clinical safety and efficacy of IS in high-risk groups. IS has been successfully used as treatment for rheumatoid arthritis patients[10] and ID-sensitive patients.[11] IS has also been used extensively in pediatric patients and pregnant and postpartum patients.[12] The randomized clinical trial study of Kosch et al[13] revealed absolutely no differences in efficacy, toxicity, or complications of IS or IG, despite the fact that iron sucrose was administered as a 250-mg monthly dose while IG was administered weekly in 62.5-mg doses.

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