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# High-Molecular Weight Iron Dextran: A Wolf in Sheep's Clothing?

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Parenteral iron is given to patients in a variety of formulations, including two iron dextran products known as high- (HMW) or low- (LMW) molecular weight iron dextran. Despite more risk of adverse events, HMW iron dextran is sometimes substituted for LMW iron dextran without physician knowledge for reasons of cost. A recent decision by the Centers for Medicare and Medicaid Services (CMS) to remerge J-codes for both iron dextrans may increase the unintended use of HMW iron dextran, resulting perhaps in more adverse drug events. Physicians who use parenteral iron should be aware of these practices and actively participate in formulary decisions regarding their substitution.

Recently, in Tennessee, a physician ordered LMW iron dextran (INFeD, Watson, Morristown, NJ) in a patient for iron deficiency anemia when oral iron had been ineffective and tolerated poorly. The pharmacist substituted the less expensive HMW iron dextran (Dexferrum, American Regent, Shirley, NY). Anaphylaxis shortly after receiving a test dose of HMW iron dextran was followed by death. Despite at least nine publications demonstrating higher rates of adverse drug events with HMW iron dextran[1–9] and with no publications showing contradictory results, HMW iron dextran continues to be substituted by individuals seemingly unaware of the various risk profiles among products for intravenous iron replacement. In one of these studies, the adverse event rate following administration of HMW iron dextran was 28%.[5] The reported total absolute rates of adverse drug events with parenteral iron are 38 per million doses, with life-threatening adverse drug events per million of 11.3 for HMW iron dextran, 3.3 for LMW dextran, 0.9 for ferric gluconate, and 0.6 for iron sucrose.[10] Even more worrisome is the ready substitution of HMW for LMW iron dextran because of cost, which is not a rare event. We have personally documented such occurrences where clinicians ordered LMW iron dextran and HMW iron dextran was substituted in its place. In four confirmed instances where anaphylaxis did not result in death, LMW iron dextran was subsequently administered uneventfully.

By the early 1990s, intravenous iron was used routinely to synergize with erythropoiesis stimulating agents (ESAs) for the treatment of dialysis-associated anemia. LMW and HMW iron dextrans were the only products available throughout the 1990s. In 1997, LMW iron dextran became unavailable for several months, necessitating the use of HMW iron dextran in virtually all dialysis patients requiring intravenous iron to support erythropoiesis. During that period, there was an 1100% increase in adverse drug events reported to the Food and Drug Administration (FDA) following administration of iron dextran according to data obtained through the Freedom of Information Act (obtained by M.A.). Subsequently, in 1998, the FDA declared LMW iron dextran "medically necessary" despite the widespread availability of the HMW product. The FDA definition of medically necessary is, "... if the product is used to treat or prevent a serious medical condition, and there is no other source of that product or alternative drug that is judged by medical staff to be an adequate substitute." Today, other parenteral iron products are also relatively safer, including ferric gluconate and iron sucrose, although more expensive.

In the first study to demonstrate the benefits of intravenous iron when used in conjunction with ESAs for chemotherapy-induced anemia, 79 patients received LMW iron dextran and two patients received HMW iron dextran.[9] Although none of the 79 patients receiving LMW iron dextran experienced a serious adverse drug event, one of the two patients who received HMW iron dextran experienced anaphylaxis requiring intubation. Using data from the FDA MedWatch program, Chertow *et al.*[3] determined that the rates of all, as well as life-threatening, adverse drug events were significantly higher among recipients of HMW *versus* LMW iron dextran or other nondextran iron products. Moreover, using conservative assumptions about the distribution of "iron dextran-associated" adverse drug events where product was not specified, the authors suggest the higher event rate observed with HMW iron dextran may be an underestimate. There also are two published studies in hemodialysis patients comparing LMW iron dextran to iron sucrose,[10,11] generally considered by nephrologists to be safer than iron dextran, showing some[10] or no difference in toxicity.[11]

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In 2006, different J-codes, which are drug-specific codes used to bill CMS, were assigned to Dexferrum (HMW) and INFeD (LMW) iron dextrans. Providing different J-codes forced providers to discriminate between these products and allowed better tracking of drug-specific adverse reactions. In January 2008, CMS re-merged the J-codes for HMW and LMW iron dextran. For the majority of U.S. physicians who are unaware that two iron dextrans even exist, there is high likelihood that the lower-priced HMW iron dextran will be selected by group purchasing organizations for distribution to ambulatory infusion centers and hospitals. As a result, physicians may unknowingly administer the HMW iron dextran, thereby increasing the likelihood of life-threatening, preventable adverse events. This substitution could accentuate the underutilization of intravenous iron that abounds already because of misinterpretation and misunderstanding of the incidence and nature of serious adverse events largely associated with HMW iron dextran. Given so much uncertainty surrounding the safety of ESAs in oncology as well as in nephrology practices, decreased utilization of intravenous iron would be counterproductive. There are now five publications in the oncology literature (three published and two in press),[9,12–15] demonstrating intravenous iron synergizes with ESAs in improving hemoglobin responses, decreasing the time to target hemoglobin and subsequently decreasing ESA exposure and cost of therapy. In all five of these studies, the benefits were independent of the pretreatment baseline iron parameters, including Fe/TIBC, ferritin, and bone marrow hemosiderin.

All countries in Western Europe have halted distribution of HMW iron dextran and removed the black box warning from the package insert or equivalent documents for the LMW formulation. The clinical community's larger perception of risk associated with the use of intravenous iron is antiquated and probably incorrect. While adverse event rates are driven higher by HMW iron dextran, both HMW and LMW iron dextrans, and to a lesser extent all intravenous iron formulations, suffer this stigma. HMW iron dextran is unsafe compared with other iron products and is medically unnecessary given the availability of three safer products in the United States. We urgently recommend avoiding use of HMW iron dextran in all clinical practice settings. We also recommend that the FDA withdraw this formulation of intravenous iron. Additional research into the optimal use of parenteral iron, particularly among persons treated with ESAs, is clearly warranted.

## DISCLOSURES

Drs. Rodgers, Cella, Chertow, and Glaspy have nothing to disclose. Drs. Auerbach, Coyne, and Henry are consultants for Watson Pharmaceuticals, and Dr. Coyne has received research support from Watson Pharmaceuticals.

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