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Adverse Events Associated With Intravenous Iron Preparations: A Comparison of Reported Rates

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H&O What are the most common intravenous iron preparations used in the United States?

GB Several intravenous (IV) iron preparations are widely used in the United States. Iron dextran is available in 2 variants: high-molecular weight (Dexferrum, American Regent) and low-molecular weight (INFeD, Watson). Sodium ferric gluconate is available in its original version (Ferrlecit, Sanofi-Aventis) and a newer generic formulation (Nulecit, Watson). Other preparations are iron sucrose (Venofer, American Regent/Fresenius Medical Care) and the newest agent, ferumoxytol (Feraheme, AMAG), which was approved in 2009. There are some significant differences among these iron preparations, which I will discuss.

H&O In what types of patients are IV iron preparations used?

GB Iron preparations have been widely used in the United States for several decades. Most of the experience with these preparations has been gained from patients with end-stage kidney disease undergoing treatment with hemodialysis. Since the advent of erythropoietin-stimulating agents (ESAs) in the United States in the late 1980s for the treatment of anemia associated with chronic kidney disease, clinicians have been trying to optimize therapy of these expensive preparations. ESAs are administered intravenously or subcutaneously. They stimulate the production of red blood cells through their action within bone marrow. In hemodialysis patients, interest in IV iron preparations has escalated over the past 20 years because of the ever-increasing awareness that optimal anemia management requires the ready availability of iron within bone marrow, and that judicious use of IV iron may decrease the dosing requirements of the more expensive ESAs. There has been a tremendous amount of experience in administering such agents to these patients in the past 5–10 years.

Clinicians in other fields have started to recognize that IV iron preparations might be appropriate for use in their patient populations. There has been a large increase in the use of IV irons in off-label situations, such as in patients who have significant iron deficiency anemia due to inflammatory bowel disease, chemotherapy-associated anemia, cancer-induced anemia, heavy uterine bleeding, congestive heart failure, the postpartum period, or earlier stages of chronic kidney disease (especially stage 4). The number of patients in these populations far exceeds that of patients who are undergoing hemodialysis. It is possible that as clinicians become more familiar with the use of IV iron preparations in those conditions—and as clinical practice guidelines address them—hemodialysis patients will come to represent a small fraction of IV iron preparation use.

H&O Is there a standard approach to the use of these agents?

GB In hemodialysis patients, such as patients with end-stage kidney disease on dialysis therapy, there is a relatively standard approach. Most patients tend to have any iron deficiency addressed first, with some form of an initial loading regimen and a regular weekly or biweekly dosing of IV iron that is maintained thereafter. However, in off-label use, there is no standard approach.

Table 1. Serious and Major Adverse Events

Serious Adverse Events
Pulmonary embolism
Anaphylaxis
Unresponsiveness
Loss of consciousness
An event that resulted in hospitalization or disability
An event that was otherwise considered life-threatening
Major Adverse Events
Circulatory collapse
Hypotension
Anaphylactoid reaction
Dyspnea
Pruritus
Hypersensitivity
Urticaria

H&O What was the design of your recent study on adverse events associated with IV iron in the United States?

GB This study, which appeared in the *American Journal of Health System Pharmacy*, was designed to compare the rates of spontaneously reported adverse events associated with all of the intravenous iron agents used in the United States, including the most recently approved agent, ferumoxytol. The other agents were iron dextran, iron sucrose, and ferric gluconate.

I obtained a list of all adverse events associated with IV iron that were reported to the US Food and Drug Administration (FDA) from October 2009 through June 2010. The events were classified into deaths, serious adverse events (Table 1), other major adverse events, and other nonallergic adverse events. I calculated rates of adverse events by dividing the raw numbers of reported adverse events by the number of units that were sold over that period of time (this number was obtained from a commercial vendor). Because the commercial iron products contain differing amounts of iron, I standardized the rate of adverse events by calculation of a dose equivalent of 100 mg of iron. I calculated the odds ratios (ORs) and proportional reporting ratios to establish a comparator of the relative risks of adverse events.

H&O Did the adverse events vary among the different IV iron formulations?

GB There were some huge differences in the adverse event rates. For all adverse events combined, these rates ranged from 5.2 events per million 100 mg dose equivalents for iron sucrose to 746 events per million 100 mg dose equivalents for ferumoxytol. The ORs also differed substantially. The risk of adverse events was higher with ferumoxytol compared to both iron sucrose (OR, 142; $P<.0001$) and ferric gluconate (OR, 109; $P<.05$). The risk of death was 475 times higher with ferumoxytol compared to iron sucrose (OR, 475; $P<.0001$) and ferric gluconate (OR, 156; $P<.0001$). Iron dextran had higher risks for death (OR, 45; $P<.0001$), serious adverse events (OR, 4; $P=.001$), and other major adverse events (OR, 6.9; $P<.0001$) compared to iron sucrose, and higher risks for death (OR, 14.9; $P=.004$) and other major adverse events (OR, 12.7; $P<.0001$) compared to ferric gluconate. Both iron sucrose and iron gluconate had much smaller risks of all adverse events, deaths, and serious adverse events than ferumoxytol and, to a lesser extent, iron dextran.

H&O Were adverse events more likely to appear among certain patient groups?

GB The reports obtained from the FDA provided little patient demographic data or concurrent disease states, so we were unable to determine if certain groups were at greater risk. Other studies have shown that patients who have multiple allergic or hypersensitivity reactions to other drugs are more likely to experience similar adverse events when receiving iron dextran, iron sucrose, or ferric gluconate.

It is known that iron dextran is associated with a higher rate of allergic adverse events compared to sucrose or gluconate. It is believed that severe allergic adverse events are higher with iron dextran because the population of the United States is exposed to dextran as a component of many types of other materials, including food, cosmetics, and manufactured goods, and therefore people are at risk of developing hypersensitivity to this agent. Ferumoxytol is manufactured from a dextran derivative, and it is thought that it may be associated with similar adverse events as iron dextran. Although there are no supporting data, it seems likely that a patient who develops any type of allergic reaction to iron dextran is at risk of developing similar adverse events from ferumoxytol.

H&O What are the implications of your study for patient management?

GB In the United States, we are under significant financial constraints. Clinicians are trying to do the best for their patients by using the very best product, and at the same time they are under pressure to decrease costs as much as possible. Newly available agents tend to be more expensive than the agents they are replacing. In the United States, iron dextran products are less expensive than ferumoxytol and certain preparations of iron sucrose and iron gluconate.

Thus, it appears that while iron dextran products are the least expensive, they have a high risk of adverse events. Iron sucrose and ferric gluconate are more expensive, but appear to be substantially safer than iron dextran. The exact status with ferumoxytol is unclear, because while it is an expensive product, it appears to have a high risk of adverse events. The concern is that, as financial incentives in the United States become even stronger with the current financial climate, clinicians might start to use the less expensive agent, iron dextran, instead of iron sucrose or ferric gluconate. Our study clearly demonstrates that if clinicians revert to using the less expensive iron dextran, they are very likely to see an escalation in adverse events. The second major implication is that clinicians who use the new agent ferumoxytol are likely to see a significant and profound adverse event in at least 1 patient throughout the course of their practice lifetime.

Very serious allergic adverse events associated with IV iron are not common, and in clinical trials, they tend not to be seen. Adverse events are more likely to be noted in pharmacovigilance and pharmacosurveillance studies, after an agent has been available for a period of years and has amassed a significant amount of usage. There are many limitations to using spontaneous reports such as these to compare one agent versus another. Limitations revolve around problems associated with incomplete or erroneous reporting, inconsistencies in sales figures, and definitions of adverse events, among other issues. Another concern is that clinicians may be more likely to report adverse events associated with any new agent compared to agents that have been on the market for some time (the Weber effect); this may be the case for ferumoxytol. Nevertheless, this is the first study to compare these effects in all IV iron products available in the United States.

The conclusion of this study is that all IV iron agents are not the same. They have different adverse event profiles. Clinicians must be very cognizant of the different safety profiles and risks posed by IV iron agents when selecting one agent versus another.

Suggested Readings

Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health Syst Pharm*. 2012;69:310-320.

Rosner MH, Auerbach M. Ferumoxytol for the treatment of iron deficiency. *Expert Rev Hematol*. 2011;4:399-406.