Original Article

Update on adverse drug events associated with parenteral iron

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Abstract

Background. We previously compared the safety profile of three formulations of intravenous iron used during 1998–2000 and found higher rates of adverse drug events (ADEs) associated with the use of higher molecular weight iron dextran and sodium ferric gluconate complex compared with lower molecular weight iron dextran. Since that time, iron sucrose has become widely available and clinicians have gained additional experience with sodium ferric gluconate complex.

Methods. We obtained data from the United States Food and Drug Administration (FDA) on ADEs attributed to the provision of four formulations of intravenous iron during 2001–2003, including higher and lower molecular weight iron dextran, sodium ferric gluconate complex and iron sucrose. We estimated the odds of intravenous iron-related ADEs using 2 × 2 tables and the χ² test.

Results. The total number of reported parenteral iron-related ADEs was 1141 among approximately 30,063,800 doses administered, yielding a rate of 3.8 per million, or roughly 38 per million. Eleven individuals died in association with the ADE. Relative to lower molecular weight iron dextran, total and life-threatening ADEs were significantly more frequent among recipients of higher molecular weight iron dextran and significantly less frequent among recipients of sodium ferric gluconate complex and iron sucrose. We estimated the odds of intravenous iron-related ADEs using 2 × 2 tables and the χ² test.

Conclusions. The frequency of intravenous iron-related ADEs reported to the FDA has decreased, and overall, the rates are extremely low. This is the fourth report suggesting increased risks associated with the provision of higher molecular weight iron dextran. Life-threatening and other ADEs appear to be lower with the use of non-dextran iron formulations, although the cost per ADE prevented is extremely high.

Keywords: adverse drug events; iron dextran; iron sucrose; molecular weight; parenteral iron; sodium ferric gluconate complex

Anaemia continues to be a common problem in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) despite the availability of recombinant erythropoietin and related compounds [1]. Iron deficiency is the most common reason for hypo-responsiveness to erythropoietin [2], especially among haemodialysis patients. A heightened inflammatory state and other factors result in poor absorption of oral iron preparations [3], obligating the use of intravenous iron preparations in nearly all patients with ESRD. Unfortunately, early versions of intravenous iron compounds, typically complexed with dextran, were relatively poorly tolerated, with frequent adverse effects including life-threatening anaphylactic reactions. Newer iron dextrans and non-dextran iron preparations have reduced the risk of adverse drug events (ADEs).

Several reports have suggested an increased risk of ADEs associated with the use of higher molecular weight iron dextran preparations [4–6]. Observational data and clinical trials yielded conflicting data when
compiling lower molecular weight iron dextran and sodium ferric gluconate complex [7–9]. During the past three years, additional agents have become available, and clinicians have gained additional experience with existing formulations.

In a previous study, we used the United States (US) Food and Drug Administration (FDA) MedWatch data from 1998–2000 to estimate the rates of ADEs associated with two iron dextran preparations that differed by the molecular weight and structure of the dextran moiety (InFed® and Dexferrum®) and sodium ferric gluconate complex (Ferrlecit®). We showed that higher molecular weight iron dextran and sodium ferric gluconate complex were associated with higher ADE rates than lower molecular weight iron dextran, although life-threatening events were not significantly different when comparing the latter two agents [10]. In the current study, we used data from 2001–2003, providing an additional three years of experience with sodium ferric gluconate complex (no longer a ‘new agent’) and the addition of iron sucrose, an agent approved by the FDA in November 2000, to compare ADE rates by formulation. Since the average wholesale price per vial of intravenous iron differs by formulation, we also calculated the cost associated with prevention of life-threatening ADEs, if more expensive formulations were selected for universal use.

Methods

All parenteral iron-related ADEs reported to the FDA via the MedWatch system (www.fda.gov/medwatch/index.html) during the calendar years 2001–2003 were obtained from the Uppsala Monitoring Centre (UMC) in Sweden (www.who-umc.org/index2.html). The UMC is responsible for coordinating the World Health Organization’s (WHO) Adverse Reaction Database. Currently, 72 countries contribute to the WHO programme, including the US. The US FDA is the largest source of ADE reports; on a relative scale, only Australia and New Zealand report more ADEs than the US (416.1 per million inhabitants, using data averaged from 1996 to 2000). The population-adjusted rate of ADE reporting from the US FDA is approximately 33% to 150% higher than from corresponding organizations in Sweden, the United Kingdom, the Netherlands, Ireland, Denmark, Switzerland and France. Data on ADEs from participating national centres are updated quarterly or more frequently, and can be obtained from UMC for a modest fee.

As part of processing into the WHO Adverse Reaction Database, each incoming report is checked according to predefined quality criteria. Adverse reaction terms are checked against the WHO-ART and MedDRA, established systems of hierarchical terminologies used by the WHO since the inception of the Adverse Reaction Database in 1968. Deaths were reviewed in detail and duplicates eliminated. Specific ADEs were categorized according to the FDA’s system organ class criteria and summarized. Detailed demographic and clinical characteristics, including dialysis status, were not available.

The ADE rate was determined by dividing the number of overall or specific ADEs by the number of dose vials dispensed, the latter information obtained from IMS Health for a modest fee (open.imshealth.com). The vial size of sodium ferric gluconate complex (62.5 mg) is lower than the vial size of the two iron dextran preparations and the iron sucrose preparation (100 mg). Since we could not determine whether the entire vial dispensed was actually delivered, we calculated ADE rates per 100 mg iron dispensed [10].

We focused on total ADEs and life-threatening ADEs for inference testing. We classified ADEs as life threatening (death, cardiac arrest, coma and anaphylactoid reaction) and non-life-threatening ADEs (all others). We performed inference tests for any ADE reported in 10 or more individuals for one or more of the parenteral iron formulations (Table 1), per previously adopted methods [10]. Low molecular weight iron dextran (InFed® in US, Cosmofer® outside of US) was used as the referent group. The relative risks (odds ratios) of ADEs associated with high molecular weight iron dextran (Dexferrum®), sodium ferric gluconate complex (Ferrlecit®) and iron sucrose (Venofer®) use were estimated from two-by-two tables, using the Yates-corrected \( \chi^2 \) test. Confidence intervals were computed using the method of Fleiss [11]. To avoid penalties associated with multiple comparisons (4 iron formulations, 13 individual and 2 collective outcomes), we focused inference testing on 2-way comparisons for total and life-threatening ADEs.

Results

Frequency of ADEs

The total number of reported parenteral iron-related ADEs was 1141 among approximately 30 063 000 doses dispensed, yielding a rate of \( 3.8 \times 10^{-5} \), or roughly 38 per million doses. This rate is less than half that reported for the years 1998–2000 (94 per million). Eleven individuals died in association with the ADE. At least one death was reported in association with all four parenteral iron formulations.

Relative frequency of ADEs by formulation

Table 1 shows the actual number of reported ADEs associated with each specific intravenous iron formulation. The latter four columns show the odds ratios (OR) and 95% confidence intervals (95% CI) for each ADE comparing Dexferrum®, Ferrlecit® and Venofer® with InFed®, with the final column directly comparing the two non-dextran formulations. The risks of total ADEs (OR 3.2, 95% CI 2.7–3.8) and life-threatening ADEs (OR 3.4, 95% CI 2.0–5.9) were significantly increased among recipients of higher molecular weight iron dextran compared with lower molecular weight iron dextran. In contrast, total and life-threatening ADEs were less likely among recipients of sodium ferric gluconate complex and iron sucrose (Table 1).

Among individual ADEs, risks associated with Dexferrum® were consistently higher than with InFed® as well as the non-dextran iron preparations. The risks associated with Ferrlecit® and Venofer® tended to be lower than for InFed® although few reached conventional levels of statistical significance.
Table 1. Major AEs by parenteral iron formulation 2001 through 2003

<table>
<thead>
<tr>
<th>ADE</th>
<th>Ferrlecit</th>
<th>Dexferrum</th>
<th>InFed</th>
<th>Venofer</th>
<th>OR Ferrlecit vs InFed</th>
<th>OR Dexferrum vs InFed</th>
<th>OR Venofer vs InFed</th>
<th>OR Venofer vs Ferrlecit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>((n=11973800))</td>
<td>((n=2563000))</td>
<td>((n=6690000))</td>
<td>((n=8837000))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>1.0 (0.2-4.6)</td>
<td>0.3 (0.1-1.3)</td>
<td>0.2 (0.1-1.0)</td>
<td>0.5 (0.1-3.2)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>4.2 (1.4-12)</td>
<td>0.3 (0.1-1.3)</td>
<td>0.0 (0.0-0.6)</td>
<td>0.0 (0.0-1.7)</td>
</tr>
<tr>
<td>Coma</td>
<td>1</td>
<td>13</td>
<td>6</td>
<td>4</td>
<td>5.7 (2.2-14)</td>
<td>0.1 (0.0-0.6)</td>
<td>0.5 (0.2-1.7)</td>
<td>5.4 (0.8-36)</td>
</tr>
<tr>
<td>Anaphylactoid reaction</td>
<td>9</td>
<td>44</td>
<td>28</td>
<td>10</td>
<td>2.6 (0.9-7.7)</td>
<td>0.4 (0.1-1.3)</td>
<td>0.0 (0.0-0.5)</td>
<td>0.0 (0.0-1.3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23</td>
<td>22</td>
<td>25</td>
<td>5</td>
<td>2.4 (1.4-4.2)</td>
<td>0.5 (0.3-0.9)</td>
<td>0.5 (0.3-1.0)</td>
<td>0.9 (0.3-2.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>1.7 (0.3-8.7)</td>
<td>1.8 (0.5-6.3)</td>
<td>1.3 (0.3-4.8)</td>
<td>0.7 (0.2-1.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>7</td>
<td>28</td>
<td>8</td>
<td>4</td>
<td>9.1 (4.2-20)</td>
<td>0.5 (0.2-1.3)</td>
<td>0.3 (0.1-1.0)</td>
<td>0.6 (0.2-2.1)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>8</td>
<td>32</td>
<td>9</td>
<td>4</td>
<td>5.2 (2.9-9.4)</td>
<td>0.3 (0.1-0.6)</td>
<td>0.4 (0.2-0.9)</td>
<td>1.5 (0.5-3.5)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>20</td>
<td>26</td>
<td>12</td>
<td>12</td>
<td>5.7 (2.9-11)</td>
<td>0.9 (0.4-1.8)</td>
<td>0.8 (0.3-1.7)</td>
<td>0.8 (0.4-1.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>2.1 (0.9-5.1)</td>
<td>0.5 (0.2-1.2)</td>
<td>0.8 (0.3-1.8)</td>
<td>1.5 (0.6-3.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>2.4 (0.8-6.3)</td>
<td>1.0 (0.4-2.5)</td>
<td>0.3 (0.1-1.2)</td>
<td>0.3 (0.1-1.1)</td>
</tr>
<tr>
<td>Sweating</td>
<td>4</td>
<td>15</td>
<td>4</td>
<td>3</td>
<td>9.8 (3.4-28)</td>
<td>0.4 (0.1-1.7)</td>
<td>0.6 (0.1-2.3)</td>
<td>1.3 (0.3-5.9)</td>
</tr>
<tr>
<td>Total</td>
<td>232</td>
<td>331</td>
<td>269</td>
<td>175</td>
<td>3.2 (2.0-5.3)</td>
<td>0.3 (0.1-0.7)</td>
<td>0.2 (0.1-0.4)</td>
<td>0.6 (0.2-1.7)</td>
</tr>
</tbody>
</table>

aIncludes respiratory depression and bronchospasm.
bIncludes flushing, pruritus, urticaria, dermatitis and rash.

Iron dextran with no trade name provided among life-threatening reactions: coma (1), cardiac arrest (5), anaphylactoid reaction (4).

OR = odds ratio. The odds ratios are provided with 95% confidence intervals. If the confidence intervals extend beyond 1.0, the tests are not statistically significant at \( P < 0.05 \).

Discussion

The efficacy of parenteral iron to support erythropoiesis is indisputable [1] despite ongoing concerns regarding safety. Without intravenous iron, many patients on dialysis would remain anaemic, or would require extraordinarily high doses of erythropoietin, to the low-molecular-weight iron group (InFed), the agent with the absolute lowest life-threatening ADE rate of 0.6 per million for Venofer (and roughly six fewer deaths) per year in the US if we were to assign all 126 iron-dextran-related ADEs to the low-molecular-weight iron group (InFed), the agent with the absolute lowest life-threatening ADE rate of 0.6 per million for Venofer, respectively; we would not extinguish the increase in ADE risk associated with Dexferrum compared with InFed.

Inclusion of non-specified ADEs

There were 126 iron-dextran-related ADEs (and 10 life-threatening ADEs) reported by generic name only. If we were to assign all 126 iron-dextran-related ADEs to the low-molecular-weight iron group (InFed), the agent with the absolute lowest life-threatening ADE rate of 0.6 per million for Venofer, the corresponding reduction in absolute life-threatening ADEs was 0.6 per million for Venofer and 11.3 per million for Ferrlecit, respectively. We would not extinguish the increase in ADE risk associated with Dexferrum compared with InFed.
This is the fourth observational study to document an increased risk of adverse drug events (ADEs) associated with higher molecular weight iron dextran preparations, after McCarthy et al. [5], Fletes et al. [6] and our earlier publication using FDA data from 1998 to 2000 [10]. Bailie et al. [12] recently published a report comparing ADE rates for hypersensitivity reactions (anaphylaxis, anaphylactoid reaction, urticaria and angioedema) and death associated with the use of parenteral iron. While the authors found significantly higher ADE rates for iron dextran, they unfortunately failed to distinguish between higher and lower molecular weight formulations. To our knowledge, there is no advantage to higher molecular weight iron dextran over lower molecular weight iron dextran preparations in terms of efficacy or cost. Thus, the safety concerns raised by these studies, similar in methodology but distinct temporally and geographically, should lead to consideration of restricted use of the higher molecular weight iron dextran preparation.

Adverse drug event rates associated with sodium ferric gluconate complex were considerably lower in this study than during 1998–2000, when they were approximately 5-fold higher than ADE rates associated with lower molecular weight iron dextran. These findings raise the possibility of a ‘new agent vigilance’ bias, which we had previously considered [10]. Ferrlecit® was approved by the FDA in February 1999, so that the 1998–2000 period covered the majority of the drug’s first two years in the US market. During 2001–2003, Ferrlecit® vigilance may have been diminished, and non-life-threatening reactions were probably less likely to have been reported. Venofer® was approved by the FDA in November 2000, so that 2001–2003 might be expected to be a peak time for Venofer®-related ADE reporting. It will be interesting to observe whether the ADE rate for Venofer® decreases during 2004–2006. Since iron dextran has been in use for many years, higher ADE rates cannot be explained by a new agent vigilance bias.

While many clinicians and investigators have expressed concern regarding the toxicity of intravenous iron, based on experimental studies of iron-induced oxidative stress [13,14] and the association between hyperferritinaemia and mortality observed in epidemiological studies [15,16], there is insufficient evidence to withhold intravenous iron from dialysis patients because of safety considerations. The decision of which intravenous iron formulation to select is more complex. End-stage renal disease programme-related Medicare expenditures for intravenous iron were $233 million in 2002, increasing by 31.5% in one year [17]. While the non-dextran iron formulations appear to be associated with lower ADE rates, overall ADE rates are exceptionally low. As a result, the cost per ADE prevented is extraordinarily high, here estimated at approximately $5.0–7.8 million, and the cost per life saved considerably higher – $33 million. Compared with other medical interventions, the use of iron sucrose rather than lower molecular weight iron dextran to prevent life-threatening ADEs among US haemodialysis patients would not be considered cost-effective [18]. Even if life-threatening ADE rates were underreported by 50 or 75%, or if the costs to dialysis providers were below wholesale, the costs associated with the routine use of non-dextran iron preparations in the US would be extremely high. Differences in cost in most European and other countries are more modest, so that the economic factors associated with alternative parenteral iron formulations may be less pressing.

There are several important limitations to these analyses. First, we could not express the ADE results per patient; rather, we estimated the ADE rate per dose administered and cost estimates were based on assumptions regarding average iron requirements. Second, we had no detailed clinical information on the patients treated with parenteral iron. Therefore, we could not verify whether patients had ESRD, CKD or other conditions associated with iron deficiency, although patients on dialysis account for the vast majority of intravenous iron utilized in the US. Third, several life-threatening ADEs were linked with ‘iron dextran’ without designation of a specific formulation, so that we lost precision in our estimates of cost per ADE prevented. To provide a conservative bias in comparisons with lower molecular weight iron dextran, we provided additional estimates assuming that all ADEs attributed to generic iron dextran were associated with the lower molecular weight formulation. Fourth, we could not tell whether the full dose vial of any of the formulations was routinely administered. If the ADE rate varies by dose, and the ratio of ‘delivered to discarded’ drug differs by formulation, then we may have inaccurately estimated relative ADE rates. Fifth, given the voluntary nature of ADE reporting, it is likely that all ADEs were underascertained, especially minor ADEs. Finally, marketing efforts could influence the likelihood of differential reporting of ADEs, if providers are convinced a priori that certain agents have a lower risk of side effects. Effective marketing could have explained the lower ADE rates associated with iron sucrose, although sodium ferric gluconate complex was also touted as a lower risk agent during the last era of evaluation, and had higher reported ADE rates after its release.

In summary, using data obtained from the US FDA Medwatch programme, we determined that the frequency of intravenous iron-related ADEs has decreased, and overall rates are extremely low. All agents were associated with at least one death and at least five life-threatening ADEs. This is the fourth report suggesting increased risks associated with the provision of higher molecular weight iron dextran. The risks of life-threatening and other ADEs appear to be significantly lower with the use of non-dextran iron formulations, although the cost per ADE prevented is extremely high. From the societal perspective, it is unclear which parenteral iron formulation is best. Additional studies examining surrogate injury markers (e.g. effects of oxidative stress) are required to inform the debate. In determining the optimal intravenous iron formulation...
for use in the ESRD programme, opportunity costs, as well as absolute and relative risks of ADEs should be considered.

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Conflict of interest statement. Mr Vaage-Nilsen is employed by Nebo a/s, a Danish company responsible for the marketing of CosmoFer® , a lower molecular weight iron dextran. These data were analysed independently, and no other employee or affiliate of Nebo a/s influenced the content of the manuscript. Drs Chertow, Mason and Ahlmen report no significant conflicts of interest, including stock ownership, research support or consulting agreements. Drs Chertow, Mason and Ahlmen have received honoraria for infrequent speaking engagements.

References


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