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Original Article

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Hypersensitivity reactions and deaths associated with intravenous iron preparations

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Abstract

Background. Parenteral iron therapy is an accepted adjunctive management of anaemia in kidney disease. Newer agents may have fewer severe hypersensitivity adverse events (AE) compared with iron dextrans (ID). The rate of type 1 AE to iron sucrose (IS) and sodium ferric gluconate (SFG) relative to ID is unclear. We used the US Food and Drug Administration's Freedom of Information (FOI) surveillance database to compare the type 1 AE profiles for the three intravenous iron preparations available in the United States.

Methods. We tabulated reports received by the FOI database between January 1997 and September 2002, and calculated 100 mg dose equivalents for the treated population for each agent. We developed four clinical categories describing hypersensitivity AE (anaphylaxis, anaphylactoid reaction, urticaria and angioedema) and an algorithm describing anaphylaxis, for specific analyses.

Results. All-event reporting rates were 29.2, 10.5 and 4.2 reports/million 100 mg dose equivalents, while all-fatal-event reporting rates were 1.4, 0.6 and 0.0 reports/million 100 mg dose equivalents for ID, SFG and IS, respectively. ID had the highest reporting rates in all four clinical categories and the anaphylaxis algorithm. SFG had intermediate reporting rates for urticaria, anaphylactoid reaction and the anaphylaxis algorithm, and a zero reporting rate for the anaphylaxis clinical category. IS had either the lowest or a zero reporting rate in all clinical categories/algorithm.

Conclusions. These findings confirm a higher risk for AE, especially serious type 1 reactions, with ID therapy than with newer intravenous iron products and also suggest that IS carries the lowest risk for hypersensitivity reactions.

Keywords: hypersensitivity reactions; intravenous iron; iron dextran; iron sucrose; sodium ferric gluconate; type 1 reactions

Introduction

Iron dextran has been available in the United States for over four decades [1] and in recent years, sales of intravenous iron therapy have increased steadily. The majority of this increased use has coincided with an increasing awareness of the need to use iron in combination with erythropoietic agents for optimal management of the anaemia of chronic kidney disease [K-DOQI update 2000, available at http://www.kidney.org/professionals/kdoqi/guidelines_updates/doqi_uptoc.html#an].

Three intravenous iron preparations are currently approved for use in the US: iron dextran (InFeD®, Watson Pharma, Inc.; Dexferrum®, American Regent, Inc.), sodium ferric gluconate complex in sucrose (Ferrlecit®; Watson Pharma, Inc.) and iron sucrose (Venofer®; American Regent, Inc.). Serious type 1 allergic reactions may occur more often after the administration of iron dextran than after the other two preparations, and are more often associated with fatal and life-threatening outcomes. The incidence of post-iron dextran immediate hypersensitivity reactions has been estimated as 1.1–3.2/100 treated population [2–5] while the case fatality proportion for post-iron dextran allergic episodes has been calculated as 15.8% [1]. The risk for morbidity or mortality, plus an ongoing suboptimal management of anaemia in chronic kidney disease and end-stage renal disease, may have resulted in an inadequate therapeutic approach to anaemia. For example, recent data (2003 Annual

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The authors wish it to be known that P.L. Lane died before this manuscript was completed.

Report) from the Centers for Medicare and Medicaid Services indicate that only 64% of haemodialysis patients receive intravenous iron [http://www.cms.hhs.gov/esrd/1.asp#9].

Data to fully assess the safety profiles of intravenous iron products have been difficult to acquire. Clinical study designs are limited by exclusionary patient entry criteria, small numbers of exposed subjects and short durations of treatment [6]. Consequently, there are numerous examples of important adverse events (AE) that were not seen in clinical trials, but that were discovered in reporting systems during the post-marketing phase [7]. In addition to these issues, serious type 1 reactions are rare, which makes case ascertainment difficult even in large databases. Researchers who are presented with these kinds of methodological challenges frequently rely on surveillance databases rather than formal epidemiological studies to provide risk clarification [1,8–10]. Although surveillance data are subject to various reporting biases, careful reviews of AE reporting trends that take into account existing biological and epidemiological evidence have become well-established methods in the field of pharmacovigilance [11].

This study used a publicly available source, the Freedom of Information (FOI) surveillance database administered by the US Food and Drug Administration (FDA), together with market research data, to review the AE profiles of intravenous iron preparations available in the US. The objectives of the study were to describe the recent use of intravenous iron products in the US, to create definitions for analytical tools such as AE groupings, clinical categories and an algorithm, and to examine AE reporting rates (RRs) and proportions for clinical relevance.

Subjects and methods

Data Sources

The FOI Database is released to the public on a quarterly basis by the FDA and consists of two levels. The first contains electronic abstractions of individual patient adverse event (AE) reports that are forwarded to the FDA directly or via manufacturers following the approval of a product in the US [9]. The second FOI Database level contains the actual source documents (MedWatch forms) that were sent to the FDA. Data used for this study consisted entirely of the abstracted FOI electronic database and was obtained from a data vendor (Galt Associates, Sterling, VA, USA). All AE that are reported to the FOI Database are coded by the FDA using a standard AE terminology dictionary [Medical Dictionary for Regulatory Activities (MedDRA®)] composed of standardized descriptors called preferred terms [http://www.meddramsso.com/NewWeb2003/index.htm]. MedDRA® terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers Associations. Each report in the FOI Database is associated with one or more MedDRA® preferred terms that are listed in a Reactions File. The FOI Database Reactions File can be linked to information about patient demographics, report sources, drug therapies, dates of therapeutic administration and patient outcomes [10].

AE reports were included in this study if they (a) listed one or more of four intravenous iron trade names or their corresponding generic names as either a suspect or concomitant medication; (b) had FDA receipt dates between 1 January 1997 and 30 September 2002 (the last available date at the time of study initiation); and (c) originated from a US healthcare practitioner. Searches for the study drugs (InFeD®, Dexferrum®, Ferrlecit®, Venofer® and their generic names) included exact spelling text strings as well as a variety of close misspellings.

The exact indication for the use of parenteral iron, or the type of patient to whom it was administered, was not recorded in the FOI database.

Methods used to obtain report counts

The large number of preferred terms in the MedDRA® dictionary (currently over 15 000) can lead to such diffuse coding of clinically similar events that reporting patterns may be obscured. This effect can be addressed by identifying reports through the use of clinical categories that contain multiple MedDRA® preferred terms or through the use of single or grouped MedDRA® preferred terms that are applied in logical combinations (i.e. as clinical algorithms).

Algorithms are particularly useful in locating reports of syndromes that are known to possess multiple clinical criteria in combination. For example, anaphylaxis could have been coded using only a single MedDRA® preferred term such as 'Anaphylaxis', but could also have been coded using two MedDRA® preferred terms that referred to different body systems, such as 'Hypotension' and 'Urticaria'. Thus, in addition to the clinical category for anaphylaxis, we also defined an anaphylaxis algorithm that identified any report in which there was either a single MedDRA® preferred term indicative of anaphylaxis or a combination of the typical clinical consequences of anaphylaxis plus either of two skin indicators for histamine release (urticaria and skin angioedema).

We used MedDRA® preferred-term coding to triage reports into seven analytical counts: (i) one clinical category that contained a single MedDRA® preferred term (anaphylactoid reaction); (ii) three clinical categories that contained between two and nine MedDRA® preferred terms (anaphylaxis, upper airway angioedema and urticaria); (iii) one anaphylaxis algorithm that used several clinical categories in a logical sequence to identify reports of anaphylaxis; and (iv) two large summary categories of reports that contained any reported MedDRA® preferred term referring to a medical event (all reports and all fatal reports).

Table 1 describes our clinical categories of type 1 reactions (anaphylactoid reaction, anaphylaxis, upper airway angioedema and urticaria) and lists those MedDRA preferred terms used in the definitions. Table 2 describes the MedDRA preferred terms and rules used to define the anaphylaxis algorithm.

This study followed the standard convention of totalling counts within a category or algorithm non-duplicatively (i.e. an AE report assigned to an analytical report count was always counted once for a given category, even if more

Table 1. Description and definition of clinical categories for type 1 reactions

Clinical category	Number of MedDRA® preferred terms	Description
Anaphylactoid reaction	1	Defined as the MedDRA preferred term 'Anaphylactoid Reaction'
Anaphylaxis	2	Defined as the MedDRA preferred terms 'Anaphylactic Reaction' and 'Anaphylactic Shock'
Upper airway angioedema	5	Definition includes oedema of the tongue, throat, pharynx and larynx
Urticaria	9	Definition includes hives, urticaria and equivalent terms

Table 2. Anaphylaxis algorithm

The anaphylaxis algorithm included reports with:
A single code for anaphylaxis
OR
The combination of:
A code for a clinical manifestation of systemic allergy
Bronchospasm
Circulatory collapse
Dyspnoea or stridor
Hypotension or decreased blood pressure
Syncope or loss of consciousness
Upper airway angioedema
PLUS
A skin indicator for histamine release
Urticaria
Angioedema

than one MedDRA® preferred term that was used to define the category/algorithm was present in the report). In contrast, counts across categories or algorithms could be duplicative (i.e. a single AE report that was assigned to more than one category/algorithm was counted once for each such assignment).

Estimation of exposure

No sources are available that quantify the exact magnitude of parenteral iron doses administered to patients at any one time. Some data are available that suggest the magnitude of doses administered to haemodialysis patients. Intravenous iron tends to be used in one of two ways for the management of anaemia in chronic kidney disease and end-stage renal disease. In patients with iron deficiency, as defined by contemporary clinical practice guidelines [http://www.kidney.org/professionals/kdoqi/guidelines_updates/doqi_uptoc.html#an], it is recommended to administer intravenous iron in 1 g doses, repeated until the patient is deemed iron replete. The 1 g is given as ten 100 mg doses of iron dextran [12,13] or iron sucrose [14], or as eight 125 mg doses of sodium ferric gluconate [15], in each consecutive haemodialysis session. Following repletion, treated patients should receive maintenance iron. The amount given to each patient varies depending on iron utilization and ongoing iron losses, but typically averages ~70 mg per week in haemodialysis patients [http://www.cms.hhs.gov/esrd/1.asp#9]. Of all intravenous iron used, it is unclear how much is administered as repletion *vs* maintenance doses in end-stage renal disease and chronic kidney disease, or non-nephrology patients. The dosing data for other patient groups that receive parenteral iron is unknown. Thus, we arbitrarily attributed the same average dose to all groups of patients, whether haemodialysis or not.

Because of the difference in sizes of the units of supply for the three iron formulations, we normalized dosing to 100 mg dose equivalents. Thus, product exposure was defined as the number of 100 mg dose equivalents used in the US annually for each intravenous iron therapy. Data to perform this calculation was obtained from a market research vendor (IMS Health, Plymouth Meeting, PA, USA).

Calculation of rates and proportions

The US RR for the study interval was calculated for all events, all fatal events and each of the four clinical categories and anaphylaxis algorithm for each therapy by dividing the number of all reports, the number of fatal reports or the counts for each clinical category or algorithm by the number of 100 mg dose equivalents used in the study interval. The results were expressed as the number of AE reports/million 100 mg dose equivalents. The case fatality proportion for each clinical category and algorithm was calculated by dividing the fatal report count for that clinical category or algorithm by the total report count for that clinical category or algorithm.

Results

Exposure trend over time

The total 100 mg dose equivalents in the US, per 3 month period, for the three intravenous iron treatments increased steadily over the study interval, from ~1.3 million in March 1997 to ~3.6 million in March 2003 (Figure 1). Compared with 1997, 100 mg dose equivalents for all intravenous iron treatments for 2002 increased by 78.2%. There was an overall declining trend for iron dextran use since the fourth quarter of 1999, which coincided with the introduction of sodium ferric gluconate in mid-1999 and which accelerated following the introduction of iron sucrose into the US market in the fourth quarter of 2000.

All-event and all-fatal-event reporting rates

The all-event and all-fatal-event RRs for the three iron therapies are provided in Figure 2. The all-event RRs for iron dextran, sodium ferric gluconate and iron sucrose were 29.2, 10.5 and 4.2 reports/million 100 mg dose equivalents, respectively, while the all-fatal-event RRs were 1.4, 0.6 and 0.0 reports/million 100 mg dose equivalents, respectively.

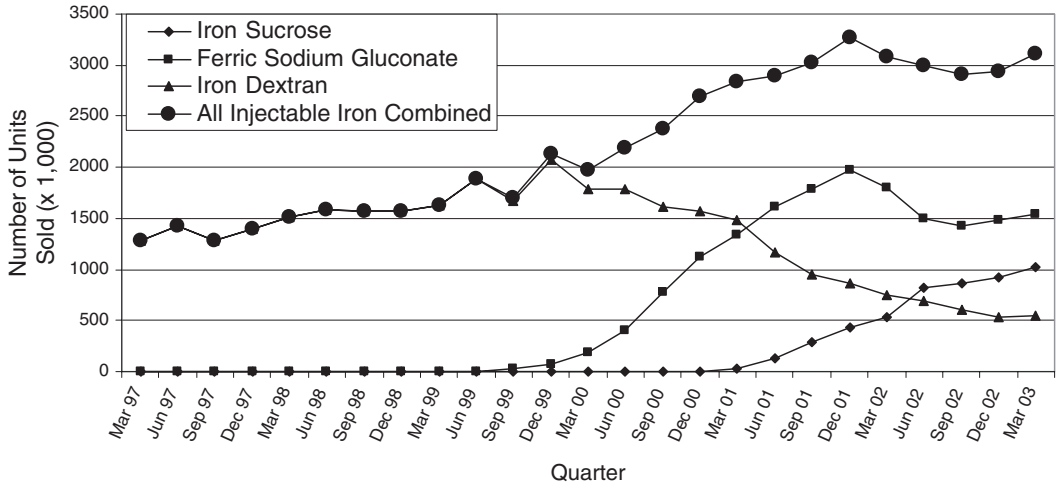

Fig. 1. Annual sales of 100 mg dose equivalents for three intravenous iron preparations in the US (January 1997–March 2003).

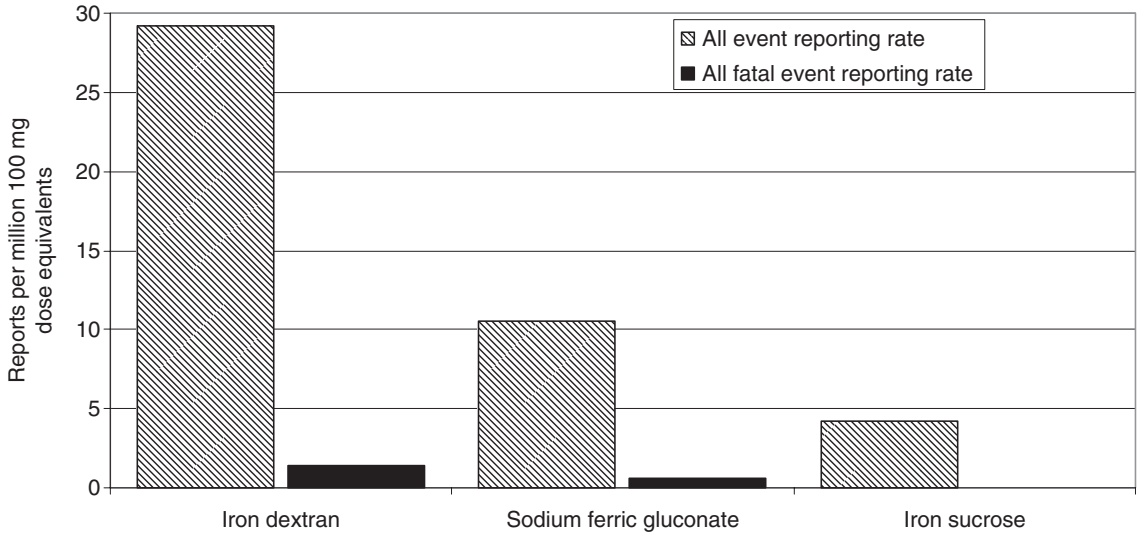

Fig. 2. Six year all-event and all-fatal-event RRs for three intravenous iron preparations in the US (January 1997–December 2002).

Clinical category reporting rates

The RRs for four clinical categories indicative of type 1 allergy are presented in Figure 3. For the category 'Urticaria', the calculated RRs for iron dextran, sodium ferric gluconate and iron sucrose were 2.1, 0.8 and 0.32 reports/million 100 mg dose equivalents, respectively. For the category 'Anaphylactoid Reaction', the corresponding RRs were 0.87, 0.46 and 0.0 reports/million 100 mg dose equivalents, respectively. The RR for iron dextran for 'Anaphylaxis' ($n = 20$) and 'Upper Airway Angioedema' ($n = 17$) were 0.6/million 100 mg dose equivalents and 0.87/million 100 mg dose equivalents, respectively. Sodium ferric gluconate had RR of 0.46 and 0.0/million 100 mg dose equivalents for 'Anaphylactoid Reaction' and 'Anaphylaxis', respectively. There were no reports in these latter categories for iron sucrose.

Algorithm reporting rate

The RR for the anaphylaxis algorithm is presented in Figure 4. The RR for intravenous iron dextran (3.1 reports/100 mg equivalents of therapy) was the highest, followed by that for sodium ferric gluconate (0.69 reports/100 mg equivalents of therapy) and iron sucrose (0.32/100 mg equivalents of therapy).

Case fatality proportions

Case fatality proportions were calculated for the four clinical categories and the anaphylaxis algorithm (Table 3). The iron dextran anaphylaxis category exhibited a case fatality proportion of 40.0%, while the proportion for the anaphylaxis algorithm was 10.0%. Intravenous iron dextran also exhibited case fatality proportions of 10.7% for 'Anaphylactoid

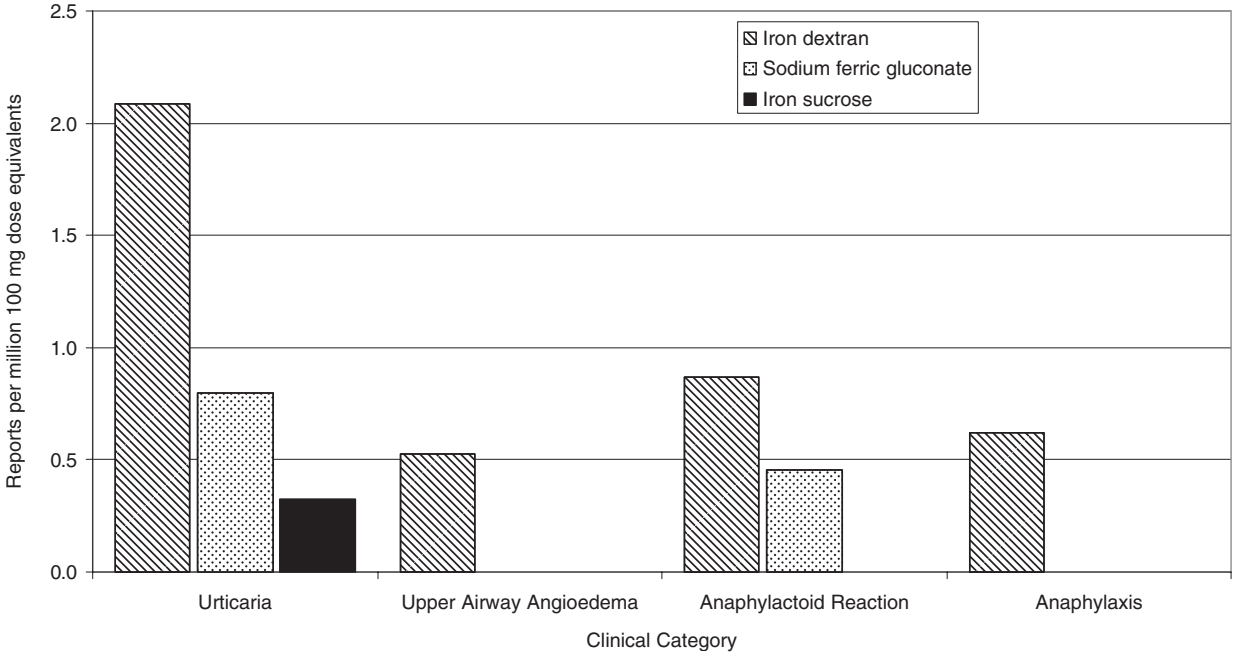

Fig. 3. Clinical category RRs for three intravenous iron therapies for type 1 reactions.

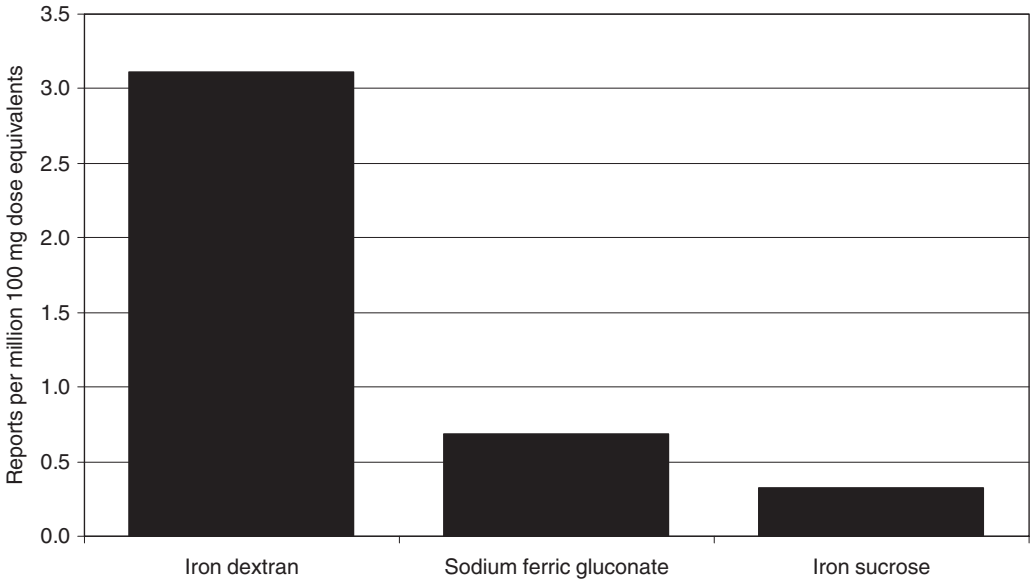

Fig. 4. Anaphylaxis algorithm RRs for three intravenous iron preparations.

Reaction' and 17.6% for 'Upper Airway Angioedema'. The case fatality proportions for sodium ferric gluconate and iron sucrose were either zero or could not be calculated (i.e. there had been no fatal or non-fatal reports to the FDA).

Discussion

Sales of intravenous iron treatments available in the US increased substantially between 1997 and 2002, and reflect two opposing trends: an overall decrease in the use of intravenous iron dextran and the increasing use of the two newer preparations. The results of both this and prior studies suggest that these trends are at least partially attributable to the AE profile of iron dextran products. Our data can be compared, to some extent, with previous findings, even though it is impossible to determine if the data from the FDA are drawn from the general population or from dialysis patients or both.

Faich and Strobos [1] used surveillance report data to investigate two major concerns that have been raised

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