

Original Article

Benchmarking iron dextran sensitivity: reactions requiring resuscitative medication in incident and prevalent patients

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Abstract

Background. Reliable information on the incidence of severe reactions to iron dextran is limited. Administration of agents of resuscitation in acute anaphylaxis may serve as a marker to quantify life-threatening adverse drug reactions.

Methods. To determine the incidence of the most serious reactions to intravenous (i.v.) iron dextran, we searched the Gambro Healthcare US medical database for evidence of same-day administration of both i.v. iron dextran and parenteral adrenaline, corticosteroids or antihistamines. We confirmed each case as an iron dextran sensitivity reaction by direct inquiry. We also determined the total reported number of suspected adverse iron dextran reactions.

Results. During the 16 month study period, we determined that 1 066 099 doses of i.v. iron dextran were given to 48 509 patients, including 20 213 patients who had not previously received iron dextran (iron dextran naïve). We identified seven patients who experienced reactions requiring resuscitative agents, all in response to a test dose (five patients) or first therapeutic dose (two patients), and therefore all in the iron-naïve (incident) group. Thus, we found the incidence of iron dextran reactions requiring resuscitative agents to be 0.035% (7 out of 20 213). No reaction was fatal. In a combined group of incident and prevalent patients, we found 337 total reports of suspected adverse reactions to iron dextran, without regard to severity of reaction, yielding an overall per patient adverse drug event (ADE) rate of 0.69% (337 out of 48 509) and per exposure rate of 0.03% (337 out of 1 066 099).

Conclusions. The incidence of reactions to iron dextran requiring resuscitative medications, per exposure or per patient, is ~0.035%. Reactions of this

severity occur after either the test dose or first dose of iron dextran.

Keywords: adverse reactions; anaemia; anaphylaxis; chronic renal failure; iron dextran; iron deficiency

Introduction

Agents administered intravenously (i.v.) for iron deficiency consist of colloidal iron-carbohydrate compounds distinguished structurally by differences in core size and carbohydrate chemistry, and clinically by differences in pharmacokinetics, maximum dose size and maximum rate of infusion [1]. That members of the iron-carbohydrate family are also distinguished by the rate of adverse reactions is frequently proposed but incompletely supported by the literature. No direct comparative studies have been performed among agents available in the USA and Europe, including iron dextran, ferric gluconate and iron sucrose. Recent prospective clinical trials have reported adverse drug events (ADEs) after ferric gluconate [2] and after iron sucrose [3]. Iron dextran reaction rates are frequently cited as a benchmark against which non-dextran iron agents are compared [2,4]. However, existing iron dextran benchmarks remain unreliable because available reports of iron dextran reaction rates lack crucial information required to calculate the true incidence and prevalence. Specifically, key studies fail to report the total number of iron dextran doses administered [5], the number of patients treated [6,7] or whether patients had been exposed to iron dextran previously [6–8].

Adverse reactions to parenteral iron agents range from minor to life-threatening. Although the clinical features of reactions to iron agents have been reviewed extensively and listed in the literature [5,9,10], information on the incidence of the most severe reactions is limited, in part because reactions described as

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anaphylactic include manifestations that are relatively benign [5], the severity of reactions described as serious is difficult to assess objectively, and the study populations upon which estimates are based have been relatively small. Moreover, because the pathogenesis of parenteral iron reactions is unknown [11], laboratory markers to distinguish degrees of severity are absent. Thus, reliable incidence information on the most severe reactions is critically needed to determine the proper role of iron dextran in anaemia management and to evaluate and compare the safety of parenteral iron agents.

Large medical databases provide powerful tools to elucidate iron dextran reactions in dialysis patients. Analysis of clinical variance reports for haemodialysis patients in the Fresenius Medical Care North America (FMCNA) database in the 6 month period October 1998–March 1999 yielded 165 suspected ADEs among 841 252 i.v. iron dextran administrations [6]. Among the 165 cases identified, 43 required emergency department evaluation, 11 were hospitalized and one died; 113 reactions occurred after the first dose in a series (maintenance or a planned course of injections); and 50% of patients with ADEs had received iron dextran safely in the past. However, because this study did not identify the total number of patients administered i.v. iron dextran, information on the incidence and prevalence of iron dextran sensitivity per patient at risk was not available, and direct comparison with results of previous reports was not possible.

To determine the incidence of the most life-threatening reactions to iron dextran in dialysis patients, we examined a large medical database containing the pharmacological treatment history of >48 000 dialysis patients who received iron dextran during a 16 month period from January 1999 to April 2000. Using medication entry fields in the database, we identified patients who received iron dextran and either adrenaline, corticosteroids or antihistamines parenterally during the same dialysis day. We reasoned that same-day administration of iron dextran and one or more of these i.v. resuscitative agents should serve as an objective marker for the most severe iron dextran reactions. We confirmed each identified episode by direct clinical inquiry and compared the number of identified episodes with the total number of i.v. iron doses given during the study period.

Patients and methods

Study design

This was a retrospective study. We searched the Gambro Healthcare database (RIMS[®]—Renal Information Management System, Gambro Healthcare, Denver, CO) for each record of i.v. iron dextran [INFeD[®]; Watson Pharmaceuticals, Corona, CA (available in Europe as Cosmofer[®]; Nebo A/S, Denmark and Vitaline Pharmaceuticals, Long Crendon, Buckinghamshire, UK) or Dexferrum[®]; American Regent, Inc., Shirley, NY (available

in Canada as DexIron[®]; Genpharm, Inc, Etobicoke, Ontario, Canada] administration in the period between January 1, 1999 and April 30, 2000. Among resulting records, we distinguished patients who had received iron dextran at any time prior to the study period from those who received iron dextran during the study period. Among patients in both groups, we then identified individuals who received i.v., subcutaneous (s.c.) or intramuscular (i.m.) administration of adrenaline, corticosteroid or antihistamine agents during a dialysis day in which iron dextran was also administered. In each resulting patient, we contacted the patient-care team directly to confirm whether the identified resuscitative agents were administered for a suspected iron dextran reaction. We also determined whether the reaction occurred after the test dose, first therapeutic dose or subsequent therapeutic doses.

To exclude the possibility that pre-treatment with either form of iron dextran would influence reactions to the other, we identified all records which included administration of both agents during the study period.

To determine the prevalence of all reactions to iron, without regard to severity, we searched for the term 'iron' or 'iron dextran' including trade names in the allergy field of the patient record. Entries in the allergy field, a component of the patient medical history file in RIMS[®], are generated by allergic reactions experienced by the patient within a Gambro dialysis facility, suffered outside the facility or reported by the patient from previous medical history.

To shed light on the incidence of all reactions to iron dextran without regard to degree of severity, we determined the total number of patients in whom adverse iron dextran reactions were reported for the first time during the study period. The search strategy specifically sought the word 'iron' or 'iron dextran' including trade names in the adverse events field of each record. We divided the result by the total number of patients who received iron dextran for the first time during the study period. We made no attempt to validate each adverse reaction report.

To assess the overall prevalence of iron dextran sensitivity in the study population, we searched the allergy field in every patient record, whether or not the patient received iron dextran during the study period, determined the number of records containing the word 'iron' and medications containing iron dextran in the allergy field, and divided the result by the total number of patients in the database.

Medical database

The Gambro Healthcare database contains the electronic medical record for every dialysis patient being treated at each out-patient Gambro facility in the USA and has several different levels of security to maintain patient confidentiality. The electronic medical record contains additional interactive functions in a relational database format propagated through Informix 7.20 (Merlo Park, CA). The resulting architecture forms the basis of the proprietary RIMS[®] software, which links data elements from patient demographics, medical history, clinical laboratory test results, medications, medical interventions and hospitalizations. Medication history includes the dose, time and date of medication administration, as well as a listing of prescribed ongoing medications. Allergies and adverse reactions are reported in distinct fields in separate components of the database: allergies as a component of the medical history, and adverse reactions to i.v. medications administered as

a component of the medication history or event reporting management system. Thus, a record of iron dextran allergy may reflect information from distant medical history obtained by interviewing the patient, and may include information on iron dextran reactions experienced either inside the Gambro facility, or at previous facilities or hospitals. Adverse reaction reports, on the other hand, include information only on those reactions that were experienced within Gambro facilities. Since adverse reaction reporting is encouraged, no attempt is made to screen serious from minor reactions.

Statistical analysis

We examined the statistical significance of the form of iron dextran used and the presence or absence of angiotensin-converting enzyme (ACE) inhibitor therapy using Poisson regression modelling (SAS Institute, Cary, NC).

Results

The Gambro Healthcare database from January 1, 1999 to April 30, 2000 contains information on a total of 61 950 dialysis patients. Our retrospective analysis yielded 1 066 099 episodes of iron dextran administration in 48 509 patients, including 28 296 patients who had received iron dextran prior to the study period (prevalent patients) and 20 213 who had not previously received iron dextran (incident patients). We identified seven episodes, in seven patients, in which i.v. iron dextran administration coincided with i.v. administration of resuscitative agents. There were no deaths. All seven episodes were confirmed as iron dextran reactions upon direct clinical inquiry. Thus, the overall per exposure rate of adverse reaction requiring resuscitative i.v. medication was 7 out of 1 066 099 (0.0007%). However, clinical inquiry determined that all seven reactions occurred after either the test dose (five patients) or first dose (two patients). Thus, among prevalent patients, there were no reactions requiring resuscitative medications. Among incident patients, where the meaningful exposures were effectively the test or first dose, the per exposure rate was equivalent to the per patient rate, or 7 out of 20 213 (0.035%).

Patients receiving INFeD[®] (five episodes in 317 097 exposures to 13 765 patients) were no more likely to experience life-threatening reactions than those receiving Dexferrum[®] (two episodes in 123 309 exposures to 6448 patients; $P=0.9733$). Patients receiving ACE inhibitor therapy were more likely to suffer a life-threatening reaction to iron dextran (either INFeD[®] or Dexferrum[®]) than patients not receiving ACE inhibitors ($P=0.0082$).

There were 337 reports of adverse reactions to iron dextran during the study period. Thus the incidence of all reported adverse iron reactions during the study period without regard to degree of severity of reaction or history of previous exposure was (337 reports out of 48 509 patients) 0.6947%. The overall per exposure adverse reaction rate was therefore (337 events out of 1 066 099 exposures) 0.0316%.

We separately analysed records in patients who received both INFeD[®] and Dexferrum[®] during the study period. Among these 2075 patients, we found no episodes of i.v. resuscitative medication administration in 76 474 iron dextran exposures.

Discussion

This report represents the second use of a large-scale medical database to elucidate iron dextran reactions, the first to determine the per patient incidence of adverse reactions to iron dextran, and the first to assess risk in incident compared with prevalent patients. The potential advantage of the current report resides in its scale, the ability to distinguish previously exposed from previously unexposed patients, and the use of an objective definition of serious iron dextran ADEs: same-day administration of iron dextran and either parenteral adrenaline, corticosteroids or antihistamines.

Our findings suggest that the most severe reactions to iron dextran are seen in naïve patients, that successful administration of a test dose does not preclude a life-threatening reaction to a first therapeutic dose, and that successful administration of a first dose seems to render the risk of developing a life-threatening reaction to subsequent doses of either form of iron dextran substantially less likely.

We used another feature of the database, the record of adverse reactions to medications, to determine the total number of iron dextran reactions serious enough to prompt withdrawal from further drug exposure. We found that adverse reactions serious enough to be reported to the database occurred in 0.7% of 48 509 dialysis patients receiving iron dextran. Previous studies conducted on a smaller scale found serious reactions in 0.7% of 573 dialysis patients [5] and 0.6% of 481 non-uraemic patients [12] examined retrospectively after iron dextran injection. The concordance between our findings and previously published results of per patient reaction rates suggests that reporting of serious adverse events to the Gambro database is relatively complete. Since the purpose of reporting to the Gambro database is to prevent further administration of iron dextran, we can consider the adverse event report rate to be equivalent to an iron dextran intolerance rate. Thus, in our mixed patient population (58% previously exposed, 42% previously unexposed), 0.7% of patients developed iron dextran intolerance over 16 months, yielding an intolerance incidence of ~0.5% per year.

We chose same-day administration of resuscitative agents as an objective marker for life-threatening reactions because broader definitions lack precision, consistency and reproducibility. Many adverse reactions to iron dextran, including rashes that satisfy published definitions of anaphylaxis, are not serious, and not all serious reactions meet criteria for anaphylaxis [5]. Some but not all patients were withdrawn from further iron dextran administration after

reactions that were not serious. Some patients who have experienced reactions described as serious, anaphylactic, anaphylactoid or allergic have not been withdrawn from further iron dextran therapy but have subsequently received multiple doses of i.v. iron dextran without adverse events [13]. Finally, some patients have experienced serious reactions to iron dextran despite successfully receiving a test dose and multiple previous therapeutic doses [5]. These observations and the paucity of information to support a single pathogenesis for all iron dextran reactions [11] argue persuasively for a single, objective standard to quantify the most serious iron dextran reactions. Our finding that resuscitative agents are required after the test dose or first dose in 0.035% of patients provides the first information on such a standard, helps to assess the role of i.v. iron dextran in the management of iron deficiency and provides a benchmark against which other parenteral iron preparations can be compared.

Our results support and extend previous findings arising from the use of a large medical database [6]. Although design differences between the two studies make direct comparison difficult, both the current and previous study show that iron dextran ADEs after iron dextran administration can be life-threatening. The previous study included one fatal ADE. Though both studies showed that most ADEs follow administration of a test dose or first dose, the previous study identified serious ADEs in patients who had successfully received previous test or treatment doses. The majority of those non-naïve patients who experienced ADEs after iron dextran administration did so at the time of the first dose of a planned series, suggesting that the risk of first-dose ADEs may recur in prevalent patients after an interval free from iron dextran exposure. The results of our analysis of adverse reaction reports without regard to degree of severity or previous iron dextran exposure (337 reports out of 1 066 099 exposures, or 0.0316%) closely approximate the results of the previous report (165 events in 841 252 exposures, rate 0.0196%) [6], which used similar ADE reports and a mixed population of incident and prevalent patients. Again, concordance between our results and those previously reported for per exposure reaction rates provide further evidence that reporting to large medical databases is relatively complete.

Assessing the quality of published evidence on the safety of i.v. iron agents requires considerable caution. Few retrospective studies provide information on a history of previous exposure [12,14], and many lack information on the number of exposures [5] or the number of patients [6]. Prospective trials may include only incident patients [3,4], only prevalent patients [15,16] or higher i.v. iron doses than are generally given [17]. We found not only that the rate of i.v. iron dextran ADEs requiring resuscitative medication is 0.035% (seven events out of 20 213 patients or exposures) but also that this risk is confined to incident patients. We conclude the obvious, that

evidence of iron safety, in the absence of specific information on numbers of doses, prevalent patients and incident patients, is unreliable and may be misleading.

Investigators recently examined the safety of iron dextran using the large voluntary reporting database of the World Health Organization [7]. Their finding that serious ADE rates for iron dextran range from 11.6 to 57.9 per million exposures is higher than that of our current study (7 per 1066 099 actual exposures) and those of others [5,6]. Either an underestimate of exposures or an increased proportion of naïve patients could explain the higher results. In the WHO study, the number of doses administered was projected and the method for calculating the projection was not completely described. Since the study period included agents new to the market, the results could also reflect a high proportion of incident patients who would therefore be at increased risk for ADEs.

Our studies provide strong support for current European Best Practice Guidelines [18] and NKF-K/DOQI [19] recommendations regarding administration of a test dose of iron dextran. These evidence-based clinical practice guidelines recommend administration of a single 25 mg test dose. Though no further test doses are required, our findings suggest that special precautions should also be taken with administration of the first therapeutic dose, and, as the previous report confirmed [6], with administration of the first dose of each newly planned series. The disproportionate risk born by incident patients suggests that introduction of i.v. iron dextran to a previously unexposed population is likely to provoke more life-threatening reactions than would be expected on the basis of previous experience with mixed populations of incident and prevalent patients. In the current study, for example, 58% of the study population consisted of prevalent patients previously exposed to iron dextran. Thus, if the entire study population had been iron dextran naïve, the projected number of life-threatening reactions encountered would have been 2- to 3-fold higher. Taken together, our findings and those of others prompt the conclusion that caution and, in particular, ready access to resuscitative medication, should attend each administration of iron dextran.

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References

1. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol* 2004; 15 [Suppl 2]: S93–S98
2. Michael B, Coyne DW, Fishbane S *et al.* Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. *Kidney Int* 2002; 61: 1830–1839

3. Charytan C, Levin N, Al Saloum M, Hafeez T, Gagnon S, Van Wyck DB. Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial. *Am J Kidney Dis* 2001; 37: 300–307
4. Coyne DW, Adkinson NF, Nissenson AR *et al.* Sodium ferric gluconate complex in hemodialysis patients. II. Adverse reactions in iron dextran-sensitive and dextran-tolerant patients. *Kidney Int* 2003; 63: 217–224
5. Fishbane S, Ungureanu VD, Maesaka JK, Kaupke CJ, Lim V, Wish J. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; 28: 529–534
6. Fletes R, Lazarus JM, Gage J, Chertow GM. Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am J Kidney Dis* 2001; 37: 743–749
7. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant* 2004; 19: 1571–1575
8. Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK. The evaluation of iron status in hemodialysis patients. *J Am Soc Nephrol* 1996; 7: 2654–2657
9. Bailie GR, Johnson CA, Mason NA. Parenteral iron use in the management of anemia in end-stage renal disease patients. *Am J Kidney Dis* 2000; 35: 1–12
10. Sunder-Plassmann G, Horl WH. Safety aspects of parenteral iron in patients with end-stage renal disease. *Drug Safety* 1997; 17: 241–250
11. Van Wyck DB. Value of a test dose of iron dextran. *Semin Dialysis* 1999; 12: 53
12. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. *J Am Med Assoc* 1980; 243: 1726–1731
13. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. *J Am Med Assoc* 1980; 243: 1726–1731
14. Wallerstein RO. Intravenous iron–dextran complex. *Blood* 1968; 32: 690–695
15. Folkert VW, Michael B, Agarwal R *et al.* Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher-dose (> or =250 mg) administration. *Am J Kidney Dis* 2003; 41: 651–657
16. Michael B, Coyne DW, Folkert VW, Dahl NV, Warnock DG. Sodium ferric gluconate complex in haemodialysis patients: a prospective evaluation of long-term safety. *Nephrol Dial Transplant* 2004; 19: 1576–1580
17. McCarthy JT, Regnier CE, Loebertmann CL, Bergstralh EJ. Adverse events in chronic hemodialysis patients receiving intravenous iron dextran—a comparison of two products. *Am J Nephrol* 2000; 20: 455–462
18. SECTION III. Treatment of renal anaemia. *Nephrol Dial Transplant* 2004; 19: II16–II31
19. IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000. *Am J Kidney Dis* 2001; 37: S182–S238

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