Intravenous iron sucrose for children with iron deficiency anemia: a single institution study

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Background: **Intravenous iron sucrose is not recommended by its manufacturers for use in children despite extensive safety and efficacy data in adults.**

Methods: **We reviewed the experience of our department between January, 2011 and February, 2014 with the use of intravenous iron sucrose in children ≤14 years of age who failed in oral iron therapy for iron deficiency anemia (IDA).**

Results: **Twelve children (6 females) aged 1.2-14 years (median age 8.9 years) received at least one dose of intravenous iron sucrose. Ten patients had IDA inadequately treated or non-responsive to oral iron therapy. One patient received therapy for blood transfusion avoidance and one for presumed iron refractory iron deficiency anemia (IRIDA). Iron sucrose infusions were given on alternate days up to three times per week. The number of infusions per patient ranged from 2 to 6 (median, 3), the individual doses from 100 mg to 200 mg (median, 200 mg), and the total doses from 200 mg to 1200 mg (median, 400 mg). Iron sucrose was effective in raising the hemoglobin concentration to normal in all patients with IDA, i.e., from 7.6±2.38 g/dL to 12.4±0.64 g/dL, within 31-42 days after the first infusion. The single patient with IRIDA demonstrated a 1.8 g/dL rise. Injection site disorders in three cases and transient taste perversion in one case were the only side effects.**

Conclusion: **Intravenous iron sucrose appears to be safe and very effective in children with IDA who do not respond or cannot tolerate oral iron therapy.**

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Key words: **adverse effects; iron deficiency; iron sucrose; parenteral iron**

Original article

Introduction

Iron deficiency is by far the most common cause of anemia worldwide.[1] Iron deficiency anemia (IDA) is particularly common in toddlers and teenage girls. In the first group, it is usually due to poor oral iron intake, as a result of consumption of large amounts of unfortified cow's milk that is also frequently associated with occult gastrointestinal bleeding.[2] In teenage girls, IDA is due to the regular and occasionally excessive blood loss associated with menstrual periods coupled with inadequate dietary iron intake. Finally, IDA is common in a variety of gastrointestinal diseases associated with chronic blood loss.

Although traditionally, oral iron therapy is the recommended treatment for IDA, oral iron therapy requires good patient adherence for several weeks, something that is frequently unachievable, since all oral iron preparations have an unpleasant metallic taste that children dislike. Moreover, if IDA is due to an inflammatory enteropathy, oral iron intake may exacerbate gastrointestinal symptoms by promoting the formation of hydroxyl radicals in the gut.[3]

Intravenous (IV) iron is an infrequently used therapeutic alternative to oral iron for the treatment of IDA in children, and even well-established medical textbooks until recently advised against parenteral iron use unless severe malabsorption or a life threatening condition was present.[4] Although various IV iron preparations have been used in adults for several decades with a good safety profile, the pediatric community has been slow in adopting parenteral iron

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use as a therapeutic option in children with moderate to severe IDA due to the serious, mainly anaphylactic reactions recorded in the past with the use of colloidal ferric hydroxide and high molecular weight iron dextran preparations.[5]

Various IV iron formulations are commercially available nowadays, with substantial pharmacological differences. Among all available parenteral iron preparations, the largest experience has been gained with the use of iron sucrose, i.e., a ferric iron-hydroxide sucrose complex. It has been extensively used for correction of IDA in patients with chronic kidney failure in combination with erythropoiesis stimulating agents.[6]

The experience with IV iron sucrose for the treatment of IDA in children is very limited, and all manufacturers do not recommend its use in children due to lack of adequate pediatric data.[7-9] We describe herein our department's experience with the use of IV iron sucrose in children with IDA that were intolerant, non-compliant or failed to respond to oral iron therapy.

Methods

We reviewed the medical records of all children aged ≤14 years, who received at least one dose of IV iron sucrose at the Department of Pediatrics of the University General Hospital of Evros for IDA between January 1, 2011 and February 28, 2014. IDA was defined as hemoglobin <2 standard deviations below the published mean normal value for age and sex[10] along with microcytic and hypochromic red cell indices, and a serum ferritin concentration of <12 ng/mL.

Patients with iron refractory iron deficiency anemia (IRIDA), a condition known to respond to parenteral iron, albeit at a much slower rate than acquired iron deficiency, were included but analyzed separately. Data collected were age and sex of all treated children, indication for parenteral iron therapy, underlying diagnoses, prior iron therapy, laboratory values before and after therapy, dosing and administration of iron sucrose, and adverse reactions recorded during or soon after administration.

In every case of IDA, the total iron deficit was estimated by using the following formula: total iron needed (mg)=[required hemoglobin (g/dL)-observed hemoglobin (g/dL)]×80 mL×body weight (kg)×0.034×1.5, where 80 mL is the volume of blood per kilogram of body weight, 0.034 is the iron content of hemoglobin (3.4%), and 1.5 is the factor used to replenish the body iron stores by adding 50% extra iron to the calculated deficit.[11]

Doses were rounded up to multiples of 100 mg. The product used was Hemafer-S®, 100 mg per 5 mL ampules for injection (Uni-Pharma Pharmaceutical Laboratories SA, Kifissia, Attica, Greece) and was diluted to normal saline by the nursing staff just before infusion to a final concentration of 1 mg/mL. The infusion was completed over 2 hours. In case of injection site pain, infusion was extended to 3 hours.

Automatic blood pressure monitoring was performed every 15 minutes for the first 30 minutes, then every 30 minutes until the end of the infusion. Medications and equipment for management of a possible anaphylactic reaction were available. Multiple infusions in the same patient were given on alternate days, up to three times per week.

Results

Twelve children (6 females) received at least one dose of IV iron sucrose during the study period. Their age ranged from 14.5 months to 14 years (median, 8.9 years). Ten patients had IDA inadequately treated with oral iron. In 9 patients, IDA was associated with poor diet with excessive milk consumption, and in one with menorrhagia. The cause of IDA was never clarified in a 9-year-old immigrant boy from Russia, who had failed oral iron therapy. All patients treated in the past with oral iron demonstrated poor adherence or gastrointestinal side effects that led to discontinuation of oral therapy. In five patients (patient 6, 7, 9, 10, and 12), screening for celiac disease with serum anti-transglutaminase antibodies was negative. One patient received IV iron sucrose due to recently diagnosed celiac disease associated with malabsorption of oral iron. A 14.5 month old female with severe IDA (patient 3) due to prolonged breastfeeding without oral iron supplementation and occult gastrointestinal bleeding after the introduction of cow's milk to the diet at the age of 12 months, received IV iron sucrose for blood transfusion avoidance. Finally, one patient received therapy for presumed IRIDA, although no testing of the *TMPRSS6* gene was performed to confirm this diagnosis.[12] However, the diagnosis is highly likely, because she had a very low serum iron and transferrin saturation that did not substantially improve after an oral iron challenge, along with a normal serum ferritin concentration and molecular testing ruled out hemoglobinopathies.

None of the administrations was preceded by a test dose, and no patient was pre-medicated with corticosteroids or antihistamines to avoid vasoactive reactions that could be misinterpreted as causally related to iron sucrose.[4]

The indications for iron sucrose therapy, the amount

Table. Patients' demographic data, underlying cause of IDA, amount of iron sucrose administered and individual patient response at two time-points after the initial infusion

No.	Age (y)	Sex	Underlying diagnosis or cause of IDA	Number of doses, amount per dose and total amount of iron sucrose	Pre-treatment Hb (g/dL)/ MCV (fL)	Day 14 post-treatment Hb (g/dL)/MCV (fL)	Day 31-42 post-treatment Hb (g/dL)/MCV (fL)
1	8.1	M	Celiac disease	2×200 mg/400 mg	9.5/64.1	11.3/71.0	11.9/72.3
2	5.2	M	Excessive milk consumption, poor diet	2×100 mg/200 mg	10.4/63.7	11.9/66.7	12.4/69.8
3	1.2	F	Prolonged breastfeeding, occult enteral bleeding	2×200 mg/400 mg	3.8/61.5	12.8/89.3	13.2/80.8
4	3.3	M	Poor diet	2×100 mg/200 mg	10.5/69.9	11.0/73.7	11.4/74.9
5	13	M	Cerebral palsy, poor diet	4×200 mg/800 mg	8.6/58.3	11.1/72.2	Not available
6	9.7	F	Occult gastrointestinal bleeding	4×200 mg/800 mg	5.4/79.2	10.4/84.1	12.3/84.1
7	9	M	Unknown etiology	5×200 mg/1000 mg	7.1/60.2	10.8/72.0	12.3/78.9
8	14	F	Menorrhagia, poor compliance to oral iron therapy	3×200 mg/600 mg	7.4/57.6	11.5/72.5	13.0/75.0
9	12.1	M	Excessive milk consumption, intolerance to oral iron	2×200 mg/400 mg	9.2/64.7	11.8/68.1	13.6/72.6
10	11.2	F	Poor diet and obesity	6×200 mg/1200 mg	7.6/63.5	12.2/73.6	12.4/81.4
11	5.1	F	Excessive milk consumption, poor diet	4×100 mg/400 mg	3.9/64.0	11.0/82.5	12.7/84.2
12	8.9	F	IRIDA	3×200 mg/600 mg	6.5/48.1	8.3/52.9	8.3/54.1

M: male; F: female; IDA: iron deficiency anemia; Hb: hemoglobin; MCV: mean corpuscular volume; IRIDA: iron refractory iron deficiency anemia.

of iron sucrose administered, and the hematological response in each treated patient are summarized in Table. The median pretreatment hemoglobin was 7.6±2.38 g/dL and was elevated to 11.3±0.69 g/dL, two weeks after the start of iron sucrose infusions. A further 1.1 g/dL hemoglobin increment was noted on hemograms performed 31 to 42 days after the initial infusion (median hemoglobin, 12.4±0.64 g/dL) in 10 of 11 patients with IDA and follow-up hemograms. The single patient with IRIDA demonstrated a moderate response with a rise of 1.8 g/dL in her hemoglobin that did not improve further.

Iron sucrose was well tolerated. No infusion was associated with cardiovascular or respiratory complications. Injection site disorders, i.e., burning that diminished with slower administration in two cases, and mild superficial phlebitis noted after the end of therapy in one case and managed with a topical heparinoid cream were the only undesirable effects. One patient complained of metallic test during a single infusion that subsided after the end of it, and did not recur with subsequent infusions. Finally, in the youngest patient, administration was slower but uneventful over 6 hours because of fragile peripheral IV access.

Discussion

All different IV iron preparations have a similar mechanism of action. After IV administration, the circulating iron-carbohydrate complexes are phagocytized by macrophages. Intracellularly, iron is released into a low molecular weight iron pool and either assimilated into ferritin or released into extracellular transferrin, which delivers it to its cytoplasmic receptors on erythroid precursors, leading to internalization of the iron-transferrin complex and intracellular release of iron for hemoglobin biosynthesis.[13]

Despite the similar mechanism of action, the toxicity of various IV iron preparations differs substantially, and is related to their pharmacokinetic characteristics that are directly affected by the strength of the iron-carbohydrate complex. Thus, the stronger the complex, the slower the release of iron, and the lower the risk of transferrin over-saturation with minimal risk for free iron toxicity. In this regard, lower doses, and extended or alternate day infusions that maintain a serum iron concentration below the total iron binding capacity are less toxic.[14]

The occurrence of serious adverse events with iron sucrose, low molecular weight iron dextran, and ferric gluconate has been reported to be similar with an estimated incidence of <1:200 000.[4,15-18] We used iron sucrose, because it has been the standard of care for the prevention and treatment of IDA in oncology patients,[6] those undergoing hemodialysis[19-21] and those with inflammatory bowel disease.[22] The experience with iron sucrose administration for children with IDA is very limited. Akarsu et al[7] evaluated its efficacy and safety in 62 children with IDA. The pretreatment level of hemoglobin rose from 7.9±1.2 g/dL to 11.4±1.1 g/dL three months after therapy. Mild side-effects were encountered in only 8 patients (12.9%): facial rash in 3, fever with irritability and flashing in 3, urticaria in 1, and unusual food craving in 1. Pinsk et al[8] investigated the use of IV iron sucrose in 45 children with IDA, aged 11 months to 16 years, who failed in oral iron therapy because of non-compliance. The pretreatment mean hemoglobin concentration was 7.43 g/dL (range, 5-10.1 g/dL), and

14 days after treatment it increased to 9.27±1.23 g/dL and 6 months later to 12.4±1.28 g/dL. Only one patient demonstrated temporary, reversible hypotension during treatment. Crary et al[9] reviewed 38 children with IDA aged ≤18 years treated with IV iron sucrose, excluding those with renal insufficiency. Overall, a total of 510 doses of IV iron sucrose were administered, with only six adverse reactions. Five of the reactions were mild, and the only serious reaction occurred in a patient who received 500 mg of IV iron sucrose, a dose substantially higher than the maximum daily dose recommended.

The efficacy of iron sucrose in the treatment of IDA in our series is comparable with the published results, and the treatment was effective in avoiding blood transfusions, even in patients with critically low hemoglobin concentrations. The role of IV iron in transfusion avoidance has been extensively reviewed by Auerbach et al.[23] The adverse events in our series were also similar to those described in the limited pediatric literature, and restricted to mild injection site disorders (three cases) and transient taste perversion (one case).

Regarding the doses of IV iron sucrose we used (daily 100 mg or 200 mg infusions), dose-finding studies in adults revealed that 200 mg and even 300 mg doses administered over two hours are safe, whereas 400 mg and 500 mg doses administered over the same time are associated with an excessively high rate of adverse events.[24]

Most iron sucrose infusions in our study were completed within two hours. The impact of the infusion rate on the toxicity profile of iron sucrose, i.e., 5 mg/kg given over 90 minutes and repeated 24 hours later versus 2 mg/kg administered over 3 minutes was studied in children with anemia due to chronic renal impairment. Three children in the first group developed abdominal pain, whereas six children in the second group had minor adverse events.[25] Hence, faster infusions appeared to be more toxic, although they were unlikely to be associated with serious adverse events. It is interesting that iron sucrose at 2 mg/kg per day infused daily over 2 hours has been used safely even in stable premature infants weighing <1.5 kg, resulting in a measureable augmentation of erythropoiesis beyond that of erythropoietin and oral iron alone.[14]

In the future, we will investigate the use of low molecular weight iron dextran, since limited experience shows that it may be administered as a total dose infusion with acceptable toxicity profile in children with IDA, with potential economic savings and added patient convenience.[26] Recently, a cost-minimization analysis comparing the use of iron sucrose, low-molecular-weight iron dextran and ferric carboxymaltose in adults with IDA in the National Health Service of Greece found that the use of iron sucrose was the most expensive and that of ferric carboxymaltose the least.[27] This finding is not surprising, since ferric carboxymaltose is more expensive on a mg per mg basis compared with iron sucrose or low-molecular-weight iron dextran, fewer injections are required for total iron deficit replacement.

Our study has limitations inherent to every clinical retrospective study. More specifically, the data on side-effects were derived only from the written comments of the medical records and were not systematically collected. Despite this limitation, the indication of parenteral iron therapy was set and the clinical follow-up was performed by a single pediatric hematologist, and the infusion and monitoring guidelines were consistent throughout the study period.

In conclusion, IV iron sucrose infused on alternate days over two hours until the total iron deficit is corrected is safe and effective for the treatment of IDA in children who do not respond or are intolerant or demonstrate poor adherence to oral iron therapy. More safety and efficacy studies of commercially available parenteral iron formulations that correct the total estimated iron deficit with a single infusion are needed in children.

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Ethical approval: The study is retrospective and as such does not require approval by the Ethics Committee of the Democritus University of Thrace Faculty of Medicine.

Competing interest: None.

Contributors: ME intellectualized the study and wrote the paper. TE and XV contributed to the data collection and literature search. CA approved the study and the final drafting of the manuscript. ME is the guarantor.

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