CASE REPORT

Anaphylactic Shock Secondary to Intravenous Iron Sucrose in Chronic Kidney Disease

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Abstract Intravenous (IV) iron is an essential component of therapy of anemia of chronic kidney disease (CKD). We present a rare case in which iron sucrose was infused to a patient of CKD and resulted in severe anaphylaxis and cardiac arrest minutes after starting the infusion. He was aggressively resuscitated with adrenaline and other measures following which he recovered. The use of parenteral iron is associated with several adverse drug reactions (ADR) which were seen with preparations like iron dextran but became rare with the use of newer safe preparations like iron sucrose or gluconate. The ADR can be mild or can have severe life threatening features like syncope, cardiac arrhythmias, seizures, bronchospasm and rarely cardio respiratory arrest like in our case. Iron sucrose is generally given as a IV infusion of 100–200 mg over 15–30 min and has a very low rate of ADR even with higher doses or bolus injections. But still necessary precautions and appropriate

monitoring must be done in all patients. The patients who are allergic to iron sucrose may be treated with other safer preparations or by desensitisation techniques.

Keywords Iron sucrose · Anaphylactic shock · Intravenous iron · Allergic reaction · Chronic kidney disease

Introduction

Intravenous (IV) iron therapy is an important component of therapy in anemia of chronic kidney disease (CKD). Allergic reactions were common with older iron preparations but with the advent of new safer preparations, these have become rare. We present a case of near fatal anaphylactic shock to iron sucrose (IS), to emphasise the fact that though rare, anaphylaxis can also occur with newer preparations; and discuss the various aspects related to IV iron preparations in CKD.

Case History

Forty-five years old male suffering from type 2 diabetes mellitus since 8 years, was detected to have diabetic nephropathy with evidence of non oliguric CKD. He had haemoglobin (Hb) of 8.4 g/dL (normocytic normochromic with a MCV of 76 fL), creatinine 4.9 mg/dL, urea 72 mg/dL, serum potassium 3.9 mEq/L, serum phosphate 5.5 mg/dL, 24 h urinary protein 800 mg/dL, serum albumin of 3.5 mg/dL, ultrasound showing right kidney 9.1 cm and left kidney 8.7 cm with increased corticomedullary differentiation. His glycemic control was satisfactory on human mixtard insulin (16 U before breakfast at 0800 h and 10 U before dinner at 2000 h). His iron studies

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showed serum iron 56 µg/dL, serum ferritin 22 µg/mL and transferrin saturation of 16 %, and was suggestive of iron deficiency anemia (IDA). He was initially given oral ferrous sulphate but showed a poor response after 4 weeks. He was then advised 1,000 mg of iron sucrose (total dose to be given as five injections of 200 mg twice weekly), inj recombinant erythropoietin (EPO) 4,000 IU subcutaneous twice weekly, folic acid 5 mg OD and vitamin B complex 1 tab OD. He was also taking tab alfa-calcidol 0.25 mcg OD, tab amlodipine 10 mg OD, tab metoprolol 25 mg BD, tab calcium carbonate 500 mg BD and tab pantoprazole 40 mg OD. He had no past history of use of iron injections, any past or family history of allergic diathesis.

He was started on injection IS. On the day of injection he took his routine insulin, had a normal breakfast and had no pre-existing problems. He was given injection IS 200 mg in 250 ml of normal saline (NS) over 45 min (brand SUCRON, ferric hydroxide salt, batch number AOIOI26, vial with 200/5 ml with 20 mg elemental iron per ml, manufactured in March 2011 and expiry in Feb 2014). No test dose of IS was administered. The infusion was started at the rate of 10–15 drops/minute. Within 1–2 min, the patient developed giddiness, restlessness, breathlessness and immediately lost consciousness. On examination, his pulse and blood pressure were not recordable with no spontaneous respiration. Infusion was immediately stopped and advanced cardiac life support resuscitation was provided with chest compressions and endotracheal intubation and ambu bag ventilation. His blood sugar at this time was 112 mg/dL, urgent ECG was normal with no features of hyperkalemia (which was later confirmed by a serum potassium of 4.2 mEq/L), any coronary syndrome (confirmed by serial ECGs which were normal) or any other abnormality. He was given IV adrenaline 0.1 mg (diluted in 10 ml NS) as a slow IV bolus over 5 min, along with injection hydrocortisone 200 mg, injection pheniramine maleate 22.5 mg IV and was infused 500 ml of NS rapidly over 15 min; and other resuscitative measures continued. Following 10 min, he responded with return of cardiac rhythm on cardiac monitor. He was managed in ICU setting with ventilator and inotropic support with dopamine, IV steroids and H1 and H2 blockers. He gradually improved, and was taken off mechanical ventilation within six hours and was hemodynamically stable off inotropes by 12 h. He made a complete recovery over the next 48 h.

His immunoglobulin profile showed IgE of 44 IU/mL (normal 1–87 IU/mL) with normal IgA and IgG. His eosinophil count (180/µL) and C1 esterase levels (28 mg/dL) were normal. He was subsequently discharged on oral iron and a strict advice to avoid parenteral iron.

Discussion

Anemia is common in CKD and is nearly universal in advanced CKD. The cause of anemia in CKD is multifactorial which includes relative deficiency of EPO, iron, folate or vitamin B12; diminished red blood cell (RBC) survival or hyperparathyroidism induced bone marrow fibrosis [1]. Inflammatory process in CKD also contribute to anemia by inhibiting EPO production, by causing death of immature RBCs by ligand mediated destruction and by stimulating hepatic release of hepcidin, which simultaneously blocks iron absorption in the gut and iron release from resident macrophages [2]. The treatment of anemia in CKD includes EPO analogue and hematinics like iron, folic acid and vitamin B12. Oral iron preparations are less effective in replenishing or maintaining iron stores in advanced CKD due to its poor intestinal absorption, gastrointestinal intolerance and unpredictable therapeutic response [3].

Parenteral iron is associated with risk of adverse drug reactions (ADR) which may be mild in form of fever, chills, dizziness, headache, pruritus, urticaria, nausea, vomiting, arthralgia and myalgia to severe manifestations like hypotension, syncope, cardiac arrhythmias, seizures, loss of consciousness, bronchospasm and rarely cardio respiratory arrest or even death [4]. The possible mechanisms of ADR include immune mediated mast cell hypersensitivity reaction or oxidative stress caused by bioactive partially unbound iron in the circulation. Conditions associated with low iron-binding capacity such as malnutrition, hypoproteinemic states like nephrotic syndrome, protein losing enteropathy, chronic liver disease and previous oral iron therapy or history of allergy or atopy may be at higher risk of developing ADR.

All IV iron agents are colloids that consist of spheroidal iron-carbohydrate nano particles. The core of each particle contains an iron-oxy-hydroxide gel and is surrounded by a carbohydrate shell that stabilizes the iron compound, slows the release of bioactive iron, and maintains the particles in colloidal suspension. All agents share the same core chemistry but differ from each other by the core size and the surrounding carbohydrate, which accounts for the various pharmacologic differences between them in terms of ADR and dosing. [5] Hence, lower molecular weight and stronger complexes like IS have a lower side effect profile, higher safe tolerable dose and frequent dosing regimen than higher molecular weight forms like ID.

All forms of IV iron may cause ADR. However, anaphylactic reactions appear to occur more frequently with iron dextran (ID) [6]. Fletes et al. had reported 165 ADR following 841,252 ID administrations in CKD (about 20 per 100,000 doses) amongst which 11 % required

Table 1 Comparison of rates of anaphylaxis between the various iron preparations

Type of reaction	Iron dextran	Ferric gluconate	Iron sucrose
Serious anaphylaxis	0.6–0.7 %	0.04 %	0.002 %
Hypersensitivity rate	0.2–0.3 %	0.4 %	0.005 %
Hypersensitivity per million doses	8.7	3.3	2.6
Adverse drug effects %	Up to 50	Up to 35	Up to 36

Table 2 Precautions to be taken during parenteral iron therapy

1. History of prior adverse reactions, asthma or atopy should be enquired
2. IV iron should only be administered in a hospitalised patient or in a day care centre
3. The patient should have an IV cannula in place with all the monitoring and resuscitative equipment available
4. It is preferable to administer iron sucrose as IV infusion. (Rate of infusion: 4 mg/kg/h, with about 8–10 drops for the initial 3–4 min)
5. Appropriate monitoring of vitals and watchful expectancy for ADR must be ensured
6. If any ADR appear, the infusion should be stopped and appropriate measures instituted

hospitalisation and 0.6 % died [7]. Higher adverse effect profile of ID led to the search of IS or ferric gluconate (FG) which were relatively safe as shown in Table 1.

Iron sucrose, an iron hydroxide sucrose complex in water, is administered without a test dose as IV infusion of 100 mg (maximum 200 mg) diluted in 100 ml of normal saline over 15–30 min with the rate of administration not exceeding 20 mg per minute. In a large retrospective study, with about 160,000 ampoules of IS (with 100 mg elementary iron), there were no life threatening reactions, 5–7 situations of rapidly reversible hypotension and very few minor ADR [8]. Chandler et al. examined the optimal doses of IS and found doses of 200–300 mg IV over two hours were well tolerated and safe [9]. IS has been tried as IV bolus over 2 min by Macdougall IC et al. [10] in which a total of 2,297 injections were administered, with reports of minor ADR which resolved completely within 30 min. Even though rare, anaphylactic reactions have been seen with IS and other parenteral preparations thus creating a risk of life threatening events or even death. Therefore, appropriate preventive measures should be ensured as shown in Table 2.

For patients who are allergic to IS, safer preparations such as ferric carboxymaltose, iron isomaltoside and ferumoxytol may be tried after appropriate skin testing. Oral preparations of iron may also be used. There have been

attempts of desensitisation to iron products and subsequent administration of iron products after pretreatment with corticosteroids and antihistaminics [11]. However, such reports are anecdotal and require appropriate trials to establish a definite desensitisation protocol.

Apart from CKD, parenteral iron is administered in conditions like celiac disease, antenatal cases and malabsorption and is used in various other specialities. However ADR or anaphylactic reactions though rare, can be of concern in these patients; and hence require necessary attention. The dosage and safety of parenteral iron preparations is a controversial issue in the management of anemia in CKD, as direct head-to-head comparative trials are lacking. It is therefore, imperative to be aware of these risks and to ensure necessary precautions before administering IV iron. We also recommend larger trials to compare the ADR profile of iron preparations and evaluate the underlying causes in them.

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