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Premedication protocol for iron infusions in patients with anaphylactic reaction to parenteral iron: A case series

Katheryn D. Hudon, Lemuel Sibulo, Albert M. Brady

ABSTRACT

Introduction: Iron supplementation is a mainstay of the treatment of iron deficiency that not only replenishes iron stores, but improves the life quality of the patient. Unfortunately, oral iron has myriad side effects that are intolerable for many patients, leading to iron infusion as the next step in treatment. The hypersensitivity adverse event rate for parenteral iron dextran from 1997–2002 was 29.2 reports/million, but literature for treatment of these patients is sparse.
Case Series: This report is a case study involving two female patients, 37-year-old and 31-year-old. Both females presented with severe iron-deficiency anemia while intolerant to oral iron and suffered anaphylactic reactions to parenteral iron. The method of intervention involved a premedication protocol, which was initiated immediately prior to iron sucrose infusion. For Case 1, the protocol included 10 mg IV dexamethasone, one duoneb (ipratropium bromide/albuterol sulfate), normal saline at 60 cc/hour, and 0.1 mg epinephrine given subcutaneously at the start of iron infusion, with 0.3 mg of epinephrine available at the bedside as needed for allergic reaction. For Case 2, the protocol included 50 mg IV diphenhydramine, 10 mg IV dexamethasone, one duoneb, normal saline at 50 cc/hour, 0.3 mg epinephrine at the bedside in case of reaction.
Conclusion: Patient iron levels were within normal limits after treatment, and no adverse events, such as anaphylactic reactions, occurred. With a precisely implemented premedication protocol initiated immediately prior to iron infusion, results of this case study indicate that such patients might be successfully and safely treated with parenteral iron.

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Introduction: Iron supplementation is a mainstay of the treatment of iron deficiency that not only replenishes iron stores, but improves the life quality of the patient. Unfortunately, oral iron has myriad side effects that are intolerable for many patients, leading to iron infusion as the next step in treatment. The hypersensitivity adverse event rate for parenteral iron dextran from 1997–2002 was 29.2 reports/million, but literature for treatment of these patients is sparse. Case Series: This report is a case study involving two female patients, 37-year-old and 31-year-old. Both females presented with severe iron-deficiency anemia while intolerant to oral iron and suffered anaphylactic reactions to parenteral iron. The method of intervention involved a premedication protocol, which was initiated immediately prior to iron sucrose infusion. For Case 1, the protocol included 10 mg IV dexamethasone, one duoneb (ipratropium bromide/albuterol sulfate), normal saline at 60 cc/hour, and 0.1 mg epinephrine given subcutaneously at the start of iron infusion, with 0.3 mg of epinephrine available at the bedside as needed for allergic reaction. For Case 2, the protocol included 50 mg IV diphenhydramine, 10 mg IV dexamethasone, one duoneb, normal saline at 50 cc/hour, 0.3 mg epinephrine at the bedside in case of reaction. Conclusion: Patient iron levels were within normal limits after treatment, and no adverse events, such as anaphylactic reactions, occurred. With a precisely implemented premedication protocol initiated immediately prior to iron infusion, results of this case study indicate that such patients might be successfully and safely treated with parenteral iron.

Keywords: Anaphylaxis, Iron infusion, Iron-deficiency anemia, Premedication

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INTRODUCTION

The use of iron supplementation has been increasing over the last ten or more years, perhaps due to the prevention or treatment of iron-deficiency anemia that is associated with numerous conditions such as chronic kidney disease, abnormal heavy uterine and post-partum bleeding, chronic heart failure, inflammatory bowel disease, and chemotherapy-induced anemia [1–7]. A recent study on the global burden of anemia found that though the prevalence of anemia dropped for both males and females from 1990 to 2010, the global prevalence of anemia was still at a high 32% in 2010, of which the top cause globally was iron-deficiency anemia [8]. There is also a growing recognition that an adequate body supply

of iron is important not only to avoid or treat anemia, but also to improve quality of life [9].

The most preferable route for the delivery of iron in iron-deficient patients is oral supplementation. It is simple, effective, and a relatively inexpensive method of treating conditions of iron-deficiency. On the other hand, oral iron replacement is inadequate for patients who are unable to tolerate an oral iron regimen, are unwilling to adhere to therapy, have acquired or hereditarily decreased absorption of intestinal iron, and have continuous or uncontrolled loss of blood [10, 11]. For these patients, intravenous iron administration is indicated. In a study on iron supplementation in non-dialysis chronic kidney disease patients, it was found that intravenous iron offers a feasible and effective method for reducing the burden of iron-deficiency anemia [10]. Another study comparing intravenous and oral iron administration in patients with pregnancy anemia showed that iron stores increased more efficaciously with the intravenous group than with the oral group [12]. A similar study has shown a more favorable efficacy for replenishing body iron stores when given intravenously [13].

Treatment with intravenous iron has significant drawbacks. Though it produces a better hematological response in increasing stores of body iron in comparison to the oral route, intravenous iron preparations are associated with serious side-effects, such as allergic or anaphylactic reactions [1]. It is useful to note that clinicians have different choices of intravenous iron preparations, such as iron dextran, sodium ferric gluconate complex, and iron sucrose. Studies have demonstrated that iron dextran has significantly higher proportions of anaphylactoid or anaphylaxis reactions, upper airway angioedema, and urticaria, while iron sucrose carried the lowest rate for these hypersensitivity reactions [1].

In an analysis of all hypersensitivity adverse events reported to the Food and Drug Administration from 1997–2002, the all-event reporting rate for iron dextran was 29.2 reports/million 100 mg dose equivalents, compared to 10.5 and 4.2 for sodium ferric gluconate complex and iron sucrose, respectively [1]. All-fatal-event reporting rate was highest for iron dextran, with 1.4 reports/million 100 mg dose equivalents, while only 0.6 and 0.0 for sodium ferric gluconate complex and iron sucrose, respectively [1].

Although iron sucrose has a more favorable safety profile in comparison to other intravenous iron formulations, it should be noted that a recent report highlights a fatal anaphylactic shock to iron sucrose in a pregnant woman who had severe iron deficiency and was non-compliant to oral therapy [14]. Nevertheless, numerous studies recommend iron sucrose as a relatively safe and effective option when oral iron is not sufficiently effective [12,15]. Rare, serious anaphylactic hypersensitivity reactions with iron sucrose have been reported in 0.002% of cases, whereas those for iron dextran and sodium ferric gluconate complex are 0.6-0.7% and 0.04%, respectively [16].

Sensitivity to iron dextran is a predictor of future sensitivity reactions to other iron products [17]. In light of this, multiple studies have shown that iron sucrose is harmless, well tolerated, and effective for patients who have a documented prior history of reactivity to other intravenous iron preparations [18–21]. Studies conducted to evaluate the efficacy and safety of intravenous iron sucrose in dialysis patients who showed previous sensitization to iron dextran and/or sodium ferric gluconate complex, revealed the safety of iron sucrose [19, 21]. The same was shown in chronic kidney disease patients, where none of the iron dextran-sensitive patients developed any kind of reaction to iron sucrose [20].

Prior studies have also attempted to use premedication to help reduce the rate of sensitivity reactions associated with iron dextran infusion [22]. Premedication prior to intravenous iron administration, however, is often given without any data supporting its benefit, as in the Auerbach et al. study [22]. On the contrary, in a single institution's experience with parenteral iron therapy over a five-year period (December 1999 to March 2005), premedication with acetaminophen and diphenhydramine before intravenous infusion of iron dextran demonstrated a rate of adverse event per infusion of 4.4% (4 events in 91 infusions) [23]. A rate of adverse event per infusion of 12.3% (10 events in 81 infusions) was observed in patients who did not receive premedication before infusion [23]. These data showed that whether or not a patient had received diphenhydramine or acetaminophen before iron dextran infusion affected how the infusion was tolerated, and the researchers proceeded to recommend that patients receiving iron dextran infusions be premedicated with diphenhydramine and acetaminophen [23].

Limited studies have explored premedication for patients who have a history of reaction to intravenous iron infusion. Notably, a double-blind, randomized, prospective study investigated whether premedication with methylprednisolone prevents an arthralgia-myalgia syndrome that developed in 40% of patients who were previously administered intravenous iron dextran [24]. In the study, the subjects were divided into three groups: the first group received normal saline before and after iron dextran infusion, the second received 125 mg of methylprednisolone before and normal saline after iron dextran infusion, and the third group received 125 mg of methylprednisolone before and after iron dextran infusion [24]. Only 26% of the group receiving both methylprednisolone before and after infusion showed reactions to iron dextran, while 58% were seen for the first group and 33% were seen for the second [24]. Demonstrating that the proportion and severity of the arthralgia-myalgia syndrome were reduced, the researchers concluded that 125 mg of methylprednisolone be given before and after intravenous iron dextran [24].

CASE SERIES

Two cases were treated with different forms of a premedication protocol, as follows:

Case 1

A 37-year-old Caucasian female who first presented seven years ago with severe iron-deficiency anemia (ferritin of 4 ng/mL) (normal values for females: 12–150 ng/mL) secondary to dysfunctional uterine bleeding. Oral iron was not tolerated, and neither was hormonal therapy to control the uterine bleeding, so her ferritin remained severely depressed. Parenteral iron sucrose was then administered, resulting in severe respiratory distress and laryngeal edema minutes after the infusion began. Observed by the physician, this reaction was treated promptly with IV epinephrine and resolved.

As the patient was still severely iron deficient and anemic, a premedication protocol was developed for her iron infusions. The protocol prior to iron sucrose infusion includes: 10 mg IV dexamethasone, one duoneb, normal saline to run at 60 cc/hour, and 0.1 mg epinephrine given subcutaneously at the start of iron sucrose infusion, with 0.3 mg of epinephrine available at the bedside as needed for allergic reaction. The patient did not tolerate diphenhydramine because she had previously developed tardive dyskinesia-like symptoms from the medication, so it was not included in her protocol. The epinephrine was given concomitantly with iron infusion because she developed laryngeal edema and anaphylaxis with every infusion, necessitating epinephrine quickly after the infusion began anyway.

It was of utmost importance that this premedication protocol was administered immediately prior to iron infusion. In fact, the third round of iron sucrose infusion with this premedication protocol resulted in a moderate allergic reaction due to the medications being administered a full two hours before infusion began. The protocol was amended to emphasize that the iron preparation must be ready to infuse at the time of premedication, and the patient must be admitted as an inpatient to ensure precise adherence to the protocol.

Case 2

A 31-year-old female with severe iron-deficiency anemia (ferritin of 7 ng/mL) secondary to dysfunctional uterine bleeding, intolerant to oral iron. The first administration of parenteral iron sucrose resulted in an anaphylactic reaction with respiratory distress, laryngeal edema, hives, and chest pain, successfully treated and resolved with IV diphenhydramine and solumedrol.

A premedication protocol was developed for subsequent iron infusions, as she remained severely iron deficient and anemic. The protocol to be initiated immediately prior to iron sucrose infusion includes: 50 mg IV diphenhydramine, 10 mg IV dexamethasone, one duoneb, epinephrine at the bedside in case of reaction, and normal saline to run at 50 cc/hour.

The iron levels for both patients were within normal limits after treatment; and no adverse events, such as anaphylactic or anaphylactoid reactions, were observed. Case 1 continues to receive parenteral iron sucrose with this premedication protocol without incident with a goal ferritin of 50–100 ng/mL. Case 2 continues to receive parenteral iron sucrose with this premedication protocol without incident with a goal ferritin of 50–100 ng/mL. Case 2 requires fewer infusions after being started on hormonal therapy for the dysfunctional uterine bleeding.

DISCUSSION

Treatment of iron deficiency is crucial not only in preventing or treating anemia, but in improving patient's quality of life. Many patients do not tolerate oral iron and as such are relegated to iron infusions. But how do health professionals approach the patient with severe allergic reactions to parenteral iron? We developed protocols for two such patients who subsequently tolerated parenteral iron as well as iron deficient patients without such allergies. The cornerstone of the premedication protocol utilized in these cases was IV dexamethasone, one duoneb, and either IV diphenhydramine or subcutaneous epinephrine. Subcutaneous epinephrine was substituted for IV diphenhydramine in Case 1 because she developed tardive dyskinesia-like symptoms when it was previously given, so she appropriately refused all diphenhydramine. Both patients were monitored without event for two to three hours after completion of infusion. No repeat doses of any of the medications to prevent allergic reaction were required.

CONCLUSION

These cases indicated that it is critical that these medications are administered immediately prior to iron infusion and as such, overnight admission may be necessary depending on the volume and expertise of the outpatient infusion care center. These premedication protocols were well tolerated and achieved the treatment objectives. Both patients continue to do well and tolerate their iron infusions without incident.

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Lemuel Sibulo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Albert M. Brady – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Authors declare no conflict of interest.

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