

IRON: INTRAVENOUS ADMINISTRATION

Purpose

To assure the safe and appropriate administration of intravenous iron

Population Covered

Infant, pediatric, adolescent, adult, and geriatric patients receiving intravenous iron

Definitions

Iron studies. Iron studies include ferritin, TIBC, serum iron, and percent transferrin saturation

Supplemental Information

Indications

Iron is critical for normal hemoglobin synthesis to maintain oxygen transport. Additionally, iron is necessary for metabolism and synthesis of DNA and various enzymatic processes. The total body iron content of an adult ranges from 2 to 4 grams. Approximately 2/3 is in hemoglobin and 1/3 in reticuloendothelial storage and ferritin. The administration of exogenous erythropoietin increases red blood cell production and iron utilization. The increased iron utilization and possible blood losses may lead to absolute or functional iron deficiency. Iron deficiency is absolute when the hematologic indication of iron stores are low which is determined by lab values such as ferritin, serum iron or transferrin saturation percent. Patients with functional iron deficiency do not meet laboratory criteria for absolute iron deficiency. However, when IV iron is administered, these patients will demonstrate an increase in hemoglobin/hematocrit or a dose reduction in erythropoietin with stable hemoglobin/hematocrit.

In order to determine iron deficiency, it is recommended to obtain baseline labs before beginning iron therapy. Labs should be drawn using micro-sampling for CBC, reticulocyte, and iron studies with serum ferritin.

Iron supplements are necessary when the following lab values are abnormal:

- Ferritin less than 150 mcg/ml
- Transferrin saturation less than 20%

Note: If the patient's ferritin is greater than 100 mcg/ml but less than 600 mcg/ml, iron studies need to be evaluated every four weeks if erythropoietin is initiated. The pre-existing iron levels may be reduced by 50% within one week of erythropoietin therapy.

Intravenous iron is indicated as a source of iron replacement in iron deficiency anemia if the patient:

- Is unable tolerate oral iron
- Has a malabsorption syndrome
- Is considered unreliable to continue oral iron for an extended period of time.
- Is experiencing prolonged erythropoietin therapy
- Has a need to rapidly replete iron stores to protect against future bleeding (bloodless patients)

Products

There are four intravenous preparations of iron available:

- Iron Dextran – InFed by Watson (containing 50 mg elemental iron per ml) (low molecular weight) and Dexferrum (high molecular weight) by American Regent
- Ferumoxytol – Feraheme by AMAG (30mg elemental iron/ml)
- Iron Sucrose - Venofer by American Regent (containing 20 mg elemental iron per ml)
- Sodium ferric gluconate – Ferrlecit by Sanofi-Aventis (containing 12.5 mg elemental iron per ml).

Literature has shown that, in many cases, patients receiving erythropoietin therapy are unable to keep up with iron losses via oral iron, and intravenous iron may be indicated. Intravenous iron can allow up to a five-fold erythropoietic response to significant blood loss anemia, anemia of chronic disease, or renal failure anemia in a patient on erythropoietin therapy. Approximately 25% of hemodialysis patients can be maintained on oral iron supplementation, the others require intravenous iron supplementation. The clinical response to intravenous iron may be attributed to the effect of iron mobilization from the reticuloendothelial system into red cell precursors. Because of the possible occurrence of anaphylaxis following both intramuscular and intravenous administration, parenteral administration of iron should be used only when oral iron treatment is not feasible.

Total dose iron dextran may be associated with delayed (4-48 hours) adverse reactions manifested by arthralgia, backache, myalgia, adenopathy, moderate to high fever, chills, dizziness, headache, malaise, nausea, and/or vomiting. These reactions usually subside within 3-4 days. The intensity of delayed reactions ranges from severe to mild. Patients with inflammatory joint disease appear to have a higher incidence of delayed reactions. Delayed reactions have occurred in 8% to 43% of patients receiving total dose intravenous iron dextran. Patients with inflammatory joint disease may have their delayed reactions attenuated by premedication with methylprednisolone. Increased reaction severity appears to occur with doses of greater than 250mg, especially in patients weighing less than 50 Kg. Female gender is associated with a two-fold increase in moderate to severe delayed reactions.

The incidence of reactions to iron dextran does not differ with administration rates of 2 mg/minute and 6 mg/minute. The reported incidence of reaction is the same with or without aspirin, diphenhydramine, or methylprednisolone as premedications.

Flushing and hypotension have been reported following the administration of IV iron sucrose (Venofer), ferumoxytol (Feraheme), and IV sodium ferrous gluconate (Ferrlecit) in European case reports. Potentially fatal hypersensitivity reactions characterized by cardiovascular collapse, cardiac arrest, bronchospasm, oral or pharyngeal edema, dyspnea, angioedema, urticaria, or pruritus sometimes associated with pain and muscle spasm of the chest or back have been reported rarely in patients receiving Venofer or Ferrlecit.

When iron dextran (InFed) is given parenterally, the IV route is preferred. The dose of 1000 mg per hour may be given by single injection. Iron stores can be replenished at the same time the hemoglobin deficit is corrected. Iron dextran is classified pregnancy category C. Animal data reveal that iron dextran crosses the placenta and may increase the frequency of stillbirths and fetal abnormalities, as well as a decrease in neonatal survival. While this has not been shown in humans, iron dextran should be administered to pregnant women only if benefits outweigh the risks. IV iron should not be used during the first trimester of pregnancy.

Ferrlecit was not teratogenic at doses of elemental iron up to 3.24 times the recommended human dose for a person of 50 Kg body weight. There were no adequate and well-controlled studies in pregnant women. Ferrlecit should be used during pregnancy only if the potential

benefit justifies the potential risk to the fetus. IV iron should not be used during the first trimester of pregnancy. Ferrlecit is indicated for treatment in patients age 6 years and older undergoing hemodialysis who are receiving supplemental epoetin.

Note: The safety and effectiveness of Venofer has not been studied extensively in pediatric patients.

Anaphylactic-type reactions may occur with intravenous iron. The literature supports the premise that reactions are more commonly due to the dextran component of intravenous iron rather than iron itself. Intravenous iron sucrose and sodium ferrous gluconate complex has proved to be well tolerated with significantly fewer serious adverse reactions than IV iron dextran. The adverse reactions that have occurred with IV iron dextran, iron sucrose and IV sodium ferrous gluconate are most frequently within the first five minutes of administration. These reactions are characterized by respiratory difficulty, tachycardia, hypotension, respiratory arrest, and/or cardiovascular collapse. Hypotension and flushing may occur with too rapid IV administration. Immediate reactions have occurred in 3% to 7% of patients, and life-threatening reactions have occurred in 0.6% to 1.3% of patients using high molecular weight IV iron dextran. Immediate reactions to IV sodium ferrous gluconate complex and iron sucrose have occurred in 0.44% to 0.71% of patients, and life-threatening reactions have occurred in 0.04% of patients.

Steps [→ Key Points]

I Prior to beginning intravenous iron infusion:

A. Ensure that epinephrine 1 mg/ml, 1ml ampule, is readily available prior to initiating therapy.

B. Initial pain at the infusion site is avoided by piggybacking the iron dextran into primary infusion of normal saline and by flushing the vein well after the iron dextran is completely infused.

II Dosages:

The total amount of intravenous iron necessary to restore hemoglobin and replenish iron stores may be approximated by the following formulas. For children and adults weighing more than 15 Kg, a normal hemoglobin value of 13 g/dL - 14.8 g/dL may be used. For children weighing less than 15 Kg, a value of 12 g/dL may be used. For adults, **lean body weight (lbw) should be used for the formulas.**

A. For patients with iron deficiency anemia:

Calculate the total body iron requirement by using the patient's weight, current hemoglobin and following formula:

$$\text{Iron (mg)} = 0.675 \times \text{body weight (Kg)} \times 100 - \left\{ \left[\frac{\text{Hgb}}{\mathbf{X}} \right] \times 100 \right\}$$

Where **X** = target hemoglobin range of 12-14 g/dL

B. For patients with blood loss anemia:

Some individuals sustain blood losses on an intermittent or repetitive basis. Such blood losses may occur periodically in patients with hemorrhagic diatheses (familial telangiectasia; hemophilia; gastrointestinal bleeding) and on a repetitive basis from procedures such as renal hemodialysis. Iron therapy in these patients should be directed toward replacement of the equivalent amount of iron represented in the blood loss. Quantitative estimates of the individual's periodic blood loss and hematocrit during the bleeding episode provide a convenient method for the calculation of the required iron dose.

The formula shown below is based on the approximation that 1 mL of normocytic, normochromic red cells contains 1 mg of elemental iron:

Replacement iron (in mg) = Blood loss (in mL) x hematocrit (Use Pre blood loss hematocrit)
(One Unit RBC = 300 ml)

Example: Blood loss of 500 mL with 40% hematocrit

Replacement Iron = 500 x 0.40 = 200 mg

OR

Replacement iron (in mg) = 2.145 (IBW) (goal Hgb – measured Hgb)

Replace with Venofer in adults, with Ferrlecit in pediatrics.

C. Formula for dosing IV iron dextran as single total dose infusion:

IV Iron Dextran Dose (mls.) = 0.0442 (Desired Hb - Observed Hb) x LBW + (0.26 x LBW)

Desired Hb = the target Hb in g/dl.

Observed Hb = the patient's current hemoglobin in g/dl.

LBW = Lean body weight in kg. A patient's lean body weight (or actual body weight if less than lean body weight) should be utilized when determining dosage.

For males: LBW = 50 kg + 2.3 kg for each inch of patient's height over 5 feet

For females: LBW = 45.5 kg + 2.3 kg for each inch of patient's height over 5 feet.

(Recommended desired hemoglobin 12 -14.8g/ dL)

Intravenous doses of iron dextran such as used with total dose infusions, have been associated with an increased incidence of adverse effects. The adverse effects frequently are delayed (1-2 days) reactions typified by one or more of the following symptoms: arthralgia, backache, chills, dizziness, moderate to high fever, headache, malaise, myalgia, nausea, and vomiting. The onset is usually 24-48 hours after administration and symptoms generally subside within 3-4 days. The etiology of these reactions is not known. The potential for a delayed reaction must be considered when estimating the risk/benefit of treatment.

IV IRON DOSING

	Iron Dextran	Iron Sucrose	Ferumoxytol	Sodium Ferric Gluconate Complex (Ferrlecit)
Route of Administration	IV (preferred)	IV only	IV only	IV only
IV Test Dose	25 mg over 5 minutes. Stay with patient for initial 15 minutes and observe closely for an additional 45 minutes. (Dose can be administered from the infusion bag.)	No test dose necessary	No test dose necessary	No test dose necessary
IV Dosing	Doses less than or equal to 300 mg, slow IV push at a rate not to exceed 50 mg/minute; or diluted in 100-250 ml normal saline. For administration of a total dose infusion, the total calculated dose should be diluted in 500 ml (range of 250 to 1000 ml) of normal saline. After a test infusion, the solution may be infused over 4 to 6 hours.	100mg IVP over 2-5 minutes; 100 mg/ 100ml 0.9% NS over 15 minutes; 200mg / 250ml 0.9%NS over 2 - 4 hours for a TDI of 1,000mg over a 14-day period If more than 600mg is needed for iron repletion, a transferrin saturation and serum iron levels should be drawn 72 hours after the completion weekly dose to assist in recognition of iron accumulation. Do not continue infusions unless TSAT% is less than 40%	Is approved as a 5 x 10mg push in 17 seconds	Administer 125 mg diluted in 100 ml normal saline over 60 minutes daily for 5 doses maximum per week. May need to continue to a cumulative dose of 1 gram. Transferrin saturation and serum iron levels should be drawn 48 hours after the completion of the third dose to assist in recognition of iron accumulation. Do not continue daily infusions of Ferrlecit unless the transferrin saturation is less than 40%.
→ Verify iron calculations with pharmacist.				
Pediatric Dosing	<ul style="list-style-type: none"> Greater than 10 Kg: Administer 100 mg iron dextran IV per day until total calculated dose is given. 5-10 Kg: Administer 50 mg iron dextran IV per day until the total calculated dose is given. Infants greater than 4 months but less than 5 Kg: Administer 25 mg iron dextran IV per day until the total calculated dose is given. 	Not indicated	Not indicated	<i>Greater than 6 years old:</i> <ul style="list-style-type: none"> Dose: 1.5 mg/kg IV each HD times eight doses; Max: 125 mg/dose; Info: give in combo w/ erythropoietin tx; admin. at sequential HD

For **ANAPHYLACTIC TYPE REACTIONS** (respiratory difficulty, tachycardia, hypotension, and/or cardiovascular collapse)

1. Stop IV infusion
2. Administer epinephrine according to the *Anaphylaxis/Hypersensitivity: Treatment* protocol
3. Contact the prescriber

References

Drug Therapy Topics. University of Washington Medical Center/Harborview Medical Center.

Goodnough, L.T., Skikne, B., & Brugnara, C. (2000). Erythropoietin, iron and erythropoiesis. Blood, 96(3).

Inpatient Pharmacy Guidelines. (2003). University Hospital of Arkansas, Arkansas.

Davis, J., & Hader, R. (June 2001.) Erythropoietin and IV iron protocol for all patients except open heart, dialysis, and oncology. Center for Bloodless Care, Meridian Health System. Jersey Shore Medical Center, Neptune, New Jersey.

Torres, S., Sorensen, E.R., Bliss-Holtz, J., & Neibart, R. (2001) Implication of iron in a transfusion alternative program (bloodless) in the cardiac surgery patient. Jersey Shore Medical Center, Neptune, New Jersey.

Manual

Clinical Standards Manual