Published in final edited form as:

J Infus Nurs. 2011 November ; 34(6): 374–380. doi:10.1097/NAN.0b013e3182306356.

CHELATION THERAPY FOR IRON OVERLOAD: NURSING PRACTICE IMPLICATIONS

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Abstract

Many diseases of the blood are treated with blood transfusion therapy. Chronic transfusions can cause iron overload, and, if untreated, can cause end-organ damage. Chelation therapy provides a way of treating iron overload and minimizing its adverse effects. Nurses need to understand that iron overload is a consequence of chronic blood transfusion, and they need to know what effects it has on end-organs and what treatment options are available.

INTRODUCTION

Many diseases of the blood are treated with blood transfusion therapy. While this can often correct a blood cell deficiency characteristic of diseases that destroy red blood cells or platelets for a period of time, repeated transfusions may still be required. Chronic transfusions can cause iron overload. Untreated, iron overload can cause deleterious effects on many organs, such as the liver, and the cardiac and endocrine systems.^{1–8} The effects of iron overload are visible after damage has been done, where patients have liver dysfunction, cardiomyopathy, or diabetes.^{4,6} Chelation therapy provides a viable method of treating iron overload and minimizing the adverse effects associated with iron overload. Prior to describing chelation practices, it is important for clinicians to understand the historical development of chelation therapy.

HISTORICAL BACKGROUND

In 1893, Alfred Werner, a French-Swiss chemist, developed the theory of coordination of compounds.⁹ This theory identified a process where metals bind with organic molecules, making them inactive. He won the Nobel Prize in 1913 for his process.^{9,10} This process of binding metals to organic molecules is the basis for chelation therapy. The original application of Werner's theory was within the field of industrial production, to help eliminate heavy metal contamination brought on by the industrialization. Early industrialization did not have safeguards in place to reduce occupational exposure, so contamination of workers was high. Heavy metal toxicity can occur rapidly or be a progressive process, and its symptoms, although similar to other disorders, require treatment to minimize adverse effects. In the 1920s, new paint materials were introduced that contained heavy metals including lead, and the elimination of these heavy metals was critical.⁹ The most common binding product of the time, called ethylene-diamine-tetra-acetic acid (EDTA), was made in Germany and sold globally for industrial use.⁹

Following the occupational-contamination use described above, chelating agents were used as a medical treatment during World War I, as an antidote for poison gas. British antilewisite, a chelating agent, was the antidote against arsenic-containing lewisite gas.^{9,10} In 1947, Dr. Charles Geschickter, from Georgetown University Medical Center, was caring for a cancer patient who accumulated systemic toxic nickel complexes while receiving chemotherapy. Although Dr. Geschickter successfully used EDTA on his patient, that success did not translate into common use of EDTA in clinical practice.⁹

In the 1950s, the US Navy used chelation therapy to treat workers who developed iron overload after excessive occupational exposure while painting old warships. About this time chelating agents were introduced for treatment of such disorders as Wilson's disease and cystinuria.^{9,10} In the 1960s, chelation therapy was beginning to be researched as a treatment option for the iron overload that occurs with hemochromatosis and chronic blood transfusions. Since the 1970s, chelation therapy has been used as a treatment for patients receiving chronic transfusions for diseases that destroy blood components and lead to iron overload.^{2,5,11}

IRON OVERLOAD DISORDERS

Iron overload is the result of chronic blood transfusions of red blood cells (RBC) for various blood disorders. Transfusions are needed because of a decrease in RBC production, an increase in cell destruction, or chronic blood loss.⁶ This paper will briefly describe some of the specific diseases for which transfusions are an essential part of clinical care.

β -Thalassemia Major

β -thalassemia major is a group of inherited blood disorders affecting the formation of the hemoglobin molecule. Diagnosed in early infancy, patients exhibit signs and symptoms of severe anemia, ineffective erythropoiesis, and increased iron absorption.^{1,2,5,12} Transfusion therapy is necessary to sustain life, promote growth until adolescence, improve overall quality of life, and decrease end-organ abnormalities.^{2,12} Chronic transfusion therapy may lead to cardiac iron overload, a major cause of mortality and morbidity.¹² Hepatic cirrhosis and primary liver cancer are also common, especially in the presence of a hepatitis C infection, as well as various endocrinopathies such as diabetes.²

Sickle-Cell Disease

A second blood disorder that requires chronic transfusion therapy is sickle-cell disease. Sickle-cell disease is composed of a heterogeneous group of mutations including at least 1 copy of the sickle (HbS) mutation, which alters the form of red blood cells into sickle-shaped crescents. This common genetic blood disease is most often in the form of sickle-cell anemia where a patient has 2 genes for sickle cell (HbSS). Other forms of sickle-cell disease include 1 copy of HbS combined with either an HbC (hemoglobin C) or a β -thalassemia allele.² Sickle-cell disease is characterized by chronic anemia due to intravascular malformation or sickling of red blood cells during stress or infection. Administration of blood transfusions is used to alleviate the anemia and other complications identified with sickle-cell disease.² Iron overload is an important cause of morbidity and mortality of these patients, especially those who are treated with monthly chronic red cell transfusions for sickle-cell complications like stroke.^{8,12}

Myelodysplasia

Myelodysplasia, another disease requiring chronic transfusions, is a heterogeneous group of blood disorders characterized by hemocytopenias, dysmorphic and genetically abnormal bone marrow and blood cells of the myeloid type.^{1-3,13,14} These patients also have an

increased risk of acute leukemia. The majority of patients with this disorder are 60–80 years old.^{2,3,13} Eighty percent of individuals diagnosed with this disorder have anemia and are transfusion dependent.^{2–4,12–15}

Other Anemias

Besides myelodysplastic anemia, other anemias require chronic blood transfusions. Aplastic anemia is one such disease. A number of rare diseases are also transfusion dependent. A few of these are the bone marrow failure syndromes of Diamond-Blackfan and Fanconi anemia.² Both syndromes are congenital and cause a failure of blood cell components to mature or function properly.

There are additional disorders that cause iron overload but are not due to chronic transfusion therapy. Hemochromatosis is an autosomal recessive disorder causing abnormal absorption of iron. African iron overload, fatty liver, viral hepatitis, nonalcoholic fatty liver, and metabolic syndrome are examples of other disorders that can exhibit iron overload.^{1,2,6,16}

PHYSIOLOGICAL REACTIONS

Each unit of blood transfused contains 200–250 mg of iron.^{4,11,13} With an average transfusion of 2 units, a patient could receive as much as 500 mg of iron with each episode of transfusion. Iron is an essential element within the body, and its quantity is tightly regulated physiologically.^{3,6,11–13} The body has no mechanism to excrete excess iron.^{6,11,13} For the individual receiving an occasional transfusion, the slight increase in iron would not be a problem. However, what happens to that individual who receives 2–4 units of blood every month over a 20-year span?

Two transfused units of blood per month over 1 year would equate to 24 units of blood infused. As noted above, there is 250 mg of iron per unit of blood, which would result in accumulation of 6000 mg of iron within 1 year. Consider that patient receiving 2 units of transfused blood over a 20-year span of time; he or she will have taken in 120 000 mg of iron just from the blood transfused. Because the body has no means to deal with a large amount of excess iron, it deposits iron into end-organs such as the heart, liver, and endocrine organs, which leads to the dysfunction of these end-organs. Any individual who is receiving blood transfusions and has received greater than 20 units during his or her lifetime is considered to have iron overload.^{2,6,7}

What occurs physiologically within the body? Normal RBCs have a life span of limited duration and are continuously replenished; RBCs given in a transfusion have an even shorter life span. It is the normal apoptosis of RBCs that increases the iron circulating in the body.^{3,6,7} Increased circulating iron is bound to transferrin, an iron-binding protein with an increased affinity for mobilizing ferric (Fe^{3+}) iron.¹¹ Normally this mobilization will reduce the routine excess iron stores from the body without difficulty. When iron overload occurs, the capacity of transferrin to bind with iron is exceeded, and unbound iron becomes “free” or nontransferrin bound iron (NTBI). Labile plasma iron is one form of NTBI, and it is what is taken up into the cells of end-organs of the heart, liver, endocrine, and other organs.^{4,5,7,11,12} Excess iron found in parenchymal tissues can be deleterious and lead to serious clinical sequelae, such as cardiac failure, cardiomyopathy, liver disease, hepatic fibrosis, diabetes, and even death.^{4–6,12,13} Without iron chelation, the prognosis of a person with iron overload is poor.

There are a number of ways to identify iron overload in patients (Table 1.). Some methods of evaluating iron overload are inexpensive, noninvasive, widely available, and can identify iron burden, but they are not organ specific. The simplest method of evaluating iron

overload is to count the number of RBC transfusions and/or phlebotomy units a patient has received over time.¹⁵ Phlebotomy, used to decrease the number of red cells in the body in a number of conditions, is not always well tolerated by individuals, and it may not be a viable therapy to reduce iron overload if there are problems with vascular access.^{6,16} Another simple method of evaluation is to test serum ferritin levels.^{2-4,6,11,17} Normal ranges of ferritin for a male are 12–300 nanograms (ng)/milliliter (mL), and 12–150 ng/mL for a female; however, normal value ranges may vary slightly among different laboratories. Alterations of ferritin levels can occur in the presence of inflammation, which makes the reliability of the ferritin levels questionable.^{4,6,17}

The gold standard for iron overload evaluation is a biopsy. A liver biopsy allows for end-organ evaluation of iron overload in the liver just as an endomyocardial biopsy allows for end-organ evaluation of the heart; however, both are not consistently reliable due to the nonhomogeneous iron accumulation in these organs.^{2,4,6,13,15} Both tests are expensive and invasive, which can present problems and complications.^{6,13}

The computerized tomography (CT) scan, although noninvasive and available, has its own disadvantages. Radiation exposure, expense, diminished ability to identify early iron overload, and possible false-positive readings related to other liver diseases are some of these disadvantages.^{2,4,6} Scans by magnetic resonance imaging (MRI) can view end-organs for iron overload and are noninvasive; however, these scans are expensive. Also, standardization for the scanning and evaluating of results from an MRI is not consistent across the board and must be done per machine due to variation in scanners.^{2,4,6,7,13,17}

IRON CHELATION AIMS

Once iron overload is identified in a patient, chelation therapy can be initiated to remove iron from the patient's body. Through the medications currently available, it is possible to bind with Fe⁺ molecules from the end-organs and eliminate them either through urine or feces.^{2,7,10} The molecules of chelating drugs create an attraction and compete with the parenchymal tissues in binding with the iron. With this in mind, there are 2 specific aims for chelation therapy.

The first aim of chelation therapy is to bind excess iron within the system and remove it from the body.^{1,11,12} This occurs when iron is bound at equal or greater amounts than iron intake from transfusions through either reduction therapy or maintenance therapy. Reduction therapy is when chelation is used at rates to decrease iron levels from the present state to a more acceptable level.¹¹ Depending on the source, acceptable levels are less than 1000–2500 ng/mL.^{4-6,13,15} Maintenance therapy is used to prevent further iron, over the established acceptable level for that patient, from being stored. Once an individual is established on iron chelation therapy, there is a decreased risk of developing comorbidities and an improved survival rate.^{11,14,17}

A secondary aim of therapy is to afford the individual 24-hour protection from the effects of toxic iron and reduced end-organ damage.¹¹⁻¹⁴ If there are any gaps in therapy, iron will reinsert itself into the tissue cells, and further tissue damage occurs.¹¹ Cappellini and Piga noted that as of 2007 there had been close to 600 papers published containing data regarding iron chelation in humans. Most of the data published are not the result of controlled clinical trials, but retrospective or observational studies and case studies.^{7,13,14} It has been proposed that to develop prospective studies for the evaluation of chelation therapy with identified end points of survival and decreased heart disease would be difficult due to the identification of many preexisting factors noted at baseline. Other factors that make prospective studies unlikely are the large number of subjects who would need to be observed, the number of years of observation necessary, and the large number of resources required to accomplish

this type of study.^{2,11} There are studies that have suggested that the relationship of iron burden in various organs may be patient-specific, making it difficult to evaluate the efficacy/effectiveness of the chelation treatment between patients.¹¹

TREATMENTS

There are 3 iron chelators currently in clinical use: deferoxamine (DFO), deferiprone (L1), and deferasirox (ICL670). Each has distinct efficacy, safety, and tolerability profiles. Adherence to any of them is vital to decrease iron stores (Table 2).^{2,11}

Deferoxamine (DFO)

(Desferal, Novartis Pharma Stein AG) was developed in the 1960s, introduced in 1963, and has been in clinical use since the 1970s.^{5,11,18} Considered the standard iron chelator, DFO was a breakthrough in treatment for pathological iron stores for diseases requiring blood transfusions.⁴ The active ingredient has been shown to have a strong, specific affinity for iron stored as ferritin and hemosiderin, with 100 mg of DFO binding with 8.5 mg of ferric iron.¹¹ The half-life of DFO is short, approximately 10–30 minutes, and DFO is eliminated in urine and bile.^{2,4,6,7,11,12} Once the infusion of DFO is done, the process of chelation seems to stop. Iron in urine is a result of the breakdown of red cells of macrophages, while iron in feces comes from iron chelated within the liver.²

Originally DFO was to be administered via the intramuscular (IM) route because it is poorly absorbed in the gut due to the large molecular structure. However, it was discovered that the IM route was not as effective due to rapid plasma clearance.¹¹ In the 1980s, DFO was given via slow subcutaneous (SQ) administration with good results. Continuous slow intravenous (IV) infusion is recommended for individuals with severe cardiomyopathy related to iron overload, when the patient shows intolerance to SQ administration, and when the patient is in an inpatient setting, so as to increase the rate of reduction of iron overload.^{7,12,17,18} In measuring the efficacy of iron chelation therapy with DFO, what is calculated is the percentage of the dose excreted in the iron-bound form.

The usual dose is 20–30mg/kg/day for children and 50–60mg/kg/day for adults.^{4,6,11} This is given via slow SQ infusion over 8–12 hours through an infusion pump, usually overnight, over 5–7 days.^{2,4,5,7,11,13,14} Most often, it is due to the required regimen and the high cost of the drug that causes inconsistent patient adherence to the dosing.^{2–5,8,11–14,17}

Side effects vary. Local skin reactions can include itchy erythema and mild to moderate discomfort. Systemic reactions include fever, urticaria, headache, myalgias, or arthralgias.^{4,7,11,14} In children some skeletal changes can occur, including rickets-like boney tissues or vertebra flattening. An increased risk of infection with administration of DFO has been noted as well as disturbances of hearing and vision.^{6,11,14,17} Allergies to DFO are rare.^{4,11}

Deferiprone (L1)

(Ferriprox, Apotex/Kefler, Cipla Ltd.) was synthesized and tested in the early 1980s and first used in humans in 1987 in London with individuals having myelodysplasia and thalassemia.¹¹ Currently L1 is licensed and available only in the European Union and other countries outside the United States and Canada and is approved only for thalassemia patients.^{7,11,18}

Deferiprone is used as a second line of treatment when use of DFO is contraindicated or inadequate, and in combination therapy with DFO.^{2,4,11} Deferiprone is rapidly absorbed, with a half-life of 90–160 minutes.^{4,6,11,17} Efficacy is determined by iron excreted in a 24-

hour urine specimen and serial ferritin levels.^{6,11,12} An MRI is used to measure the iron overload in the liver and heart. The standard dose is 75 mg orally 3 times a day.^{2,4,5,11} The drug primarily removes iron in cardiac cells and, to a lesser degree, promotes changes in liver iron or serum ferritin.^{2,4,11}

Some side effects related to L1 include nausea, vomiting, abdominal pain, and zinc insufficiency. Elevated hepatic transaminase and liver fibrosis have been reported but are not reproducible.^{5-7,11,14} In India, side effects of arthropathy and arthralgias have been seen. Neutropenia and agranulocytosis are the more serious side effects reported.^{4-7,11,13,14,17} Poor adherence is seen with this drug as well.

Deferasirox (1CL670)

(Exjade, Novartis Pharma Stein AG) is another oral iron chelator. It takes 2 molecules of the drug to bind with 1 molecule of Fe^{3+} .¹¹ Usually the tablets are dissolved in a liquid (water, orange, or apple juice) and given on an empty stomach 30 minutes prior to ingesting food, where it is well absorbed.⁷ The half-life of the drug is 8–16 hours, and it is rapidly absorbed.^{4,6,17} This oral preparation is approved for use in the United States, Canada, and Europe.^{6,7,11} The standard dose is 20–30 mg/kg/day in a single dose or in divided doses. Bound iron is excreted via feces.^{2,4,6,11,12,17}

The most common side effects include gastrointestinal (GI) symptoms of nausea, vomiting, and abdominal pain. A transient skin rash can be mild to moderate, and mild increases in serum creatinine are also seen.^{4,6-8,11,14,17,18} Usually poor adherence to this drug is related to the complaints of GI symptoms.

FUTURE ADVANCES IN RESEARCH

There are 3 unlicensed drugs with some animal model data and limited clinical trial data. These clinical studies involve 2 orally administered preparations, deferitritin (GT56-252) and L1NA11, and 1 parenteral preparation of deferoxamine polymers.^{2,11}

Currently available drugs are restricted to use for transfusion-dependent hemoglobinopathies and other rare anemias.¹¹ Limited numbers of pharmaceutical companies are interested in developing drugs for rare diseases as the return for research and development is small. Both the United States and Europe have passed orphan drug legislation which hopefully will broaden the interest in research.¹¹ This legislation encompasses financial incentives for companies to conduct research.

The possibility of using chelation therapy for other iron overloaded disease states needs to be considered as well as its potential use in non-iron overload disease states, such as neurodegenerative states, infections, reperfusion injury, and hyperoxia-induced lung injury.^{1,2,11,16,18-20} Another possible avenue for research is the development of formulas that have modified bioavailability, such as slow-release formulation, or compounds that combine iron chelation with antioxidant properties.^{5,11}

NURSING IMPLICATIONS

Iron chelators are infused via intravenous or subcutaneous routes through infusion pumps. The IV administration of a chelating agent should be through a dedicated line or, if access is limited, via the SQ route. Administration through the SQ route is not always a standard route of administration for medications. When using the SQ route, the nurse should follow the policies and procedures of the institution as well as standards outlined by the Infusion Nurses Society (INS) Standard for Continuous Subcutaneous Infusion and Access

Devices.²¹ Site selection follows the same sites as SQ injections; sites are rotated and should follow sites as identified by the INS *Standards of Practice*. Inclusion of the patient in site selection can enhance compliance. Many patients comply with this therapy at home. Education regarding site care, rotation of sites, signs and symptoms of infection, and who and when to notify of problems should be done each time the patient is discharged, despite how long therapy has been in place.

An important patient education point for patients starting or already on chelation therapy is the need for consistent adherence to the therapy prescribed. Patients need the message reinforced that if they do not take the medication, they will not receive the benefit of iron reduction, their iron stores will increase and lead to potentially life-threatening problems from iron overload.

SUMMARY

Iron chelation therapy is advantageous for transfusion-dependent thalassemia and hemoglobinopathies. The need to manage iron overload is vital to reduce mortality and morbidity. Understanding how iron overload occurs and its consequences on end-organs is important. Current chelation therapy is available; however, poor adherence to this therapy is noted whether related to administration regimens or side effects. Various potential advances through research are possible and promising. Prognosis is good for transfusion-dependent individuals with well-controlled iron levels through iron chelation. Medical practitioners' and nurses' understanding of chelation therapy and the education of patients/families on the use of chelation therapy in managing iron overload are important and can assist with compliance and improve outcomes.

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Biography

Ellen J. Eckes, MSN, ARNP, FNP-BC, CCRN, is a clinical nurse specialist within Advanced Practice and Outcomes Management of the Nursing and Patient Services Department for the Clinical Center at the National Institutes of Health. She oversees programs of care that include cardiovascular pulmonary medicine, infectious diseases, and musculoskeletal disorders.

Table 1**Evaluation of Iron Overload**

Method*	Advantages	Disadvantages
Count erythrocyte transfusions	Reflects total iron burden; noninvasive, universally available; prospective; inexpensive	Not organ specific
Count phlebotomy units	Reflects total iron burden; noninvasive, universally available; inexpensive	Not organ specific; retrospective
Assess serum ferritin concentration	Widely available; noninvasive; inexpensive	Not organ specific; altered by inflammation, liver disease, recent chelation, alcohol consumption, ascorbate nutriture
Evaluate bone marrow	Detects abnormal erythroblast iron ("ringed sideroblasts"); permits estimate of macrophage iron	Invasive; usually not helpful in hemochromatosis or in absence of undiagnosed anemia
Perform liver biopsy	Major target organ; "gold standard"; liver histology	Invasive; sampling errors; expensive
Perform endomyocardial biopsy	Major target organ; organ specific; heart histology	Invasive; correlation with functional studies fair
Scan by CT	Noninvasive; widely available	Involves radiation exposure; insensitive to early iron overload; common liver disorders may yield false-positive readings; expensive
Scan by MRI (T2- weighted)	Adaptable to multiple target organs; noninvasive; can detect small primary liver cancers; widely available	Sensitivity, specificity must be evaluated for each machine; various scanning, interpretation routines; expensive
Scan by MRI (T2* - weighted)	Major target organs; noninvasive; adaptable to multiple organs; greater sensitivity than T2 methods; may become preferred method for cardiac iron	Largely investigational

* Barton, 2007.²

Abbreviations: CT, computerized tomography; MRI, magnetic resonance imaging

Table 2

Characteristics of Iron Chelators

Drug	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox
Iron chelator complex	1:1	1:3	1:2
Plasma clearance half-life	20–30 minutes	53–240 minutes	1–16 hours
Oral absorption	Negligible	Peak 45 minutes	Peak 1–2.9 hours
Iron excretion	Urine and fecal	Urine	Fecal
Therapeutic daily dose; route; schedule	40 mg/kg	75 mg/kg	20 mg/kg (maximum 30 mg/kg)
Route	SQ, IV	Oral	Oral
Frequency	8–12 hours nightly for 5–7 nights weekly	3 times daily	Once daily
Advantages	Widely available; much clinical experience; inexpensive	Good chelation of cardiac, hepatic iron; much clinical experience; inexpensive	Good chelation of cardiac, hepatic iron; no growth abnormalities in children; no agranulocytosis
Disadvantages	Inadequate chelation of cardiac iron	Inadequate chelation of cardiac iron in some cases	Limited clinical experience
Adverse effects	Reactions at infusion sites; hearing, vision, growth, skeletal abnormalities; zinc deficiency; <i>Yersinia</i> infection	Agranulocytosis; transient neutropenia; arthralgias; zinc deficiency; mild gastrointestinal symptoms; mild aminotransferase elevations	Skin rash; nonprogressive elevation of serum creatinine; mild gastrointestinal symptoms; mild aminotransferase elevations; rare hearing, vision abnormalities
Penetration to tissue	+	++ to +++	++ to +++
Lowering liver Fe	+++	+	+++
Lowering heart Fe	++ (high doses)	++ to +++	++ to +++
Compliance	+ to ++	++ to +++	++ to +++

Cappellini and Piga, 2008; Barton, 2007; Brittenham, 2011.

Definitions: SQ, subcutaneous; IV, intravenous.