REVIEW ARTICLE

Iron overload in pediatric patients

Sobrecarga de hierro en pacientes pediátricos

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Abstract

In pediatrics, chronic genetic anemias such as sickle cell disease, thalassemic syndromes and, to a lesser degree, aplastic anemia, pure red cell aplasia, myelodysplastic syndromes and dyserythropoietic syndromes are characterized by high transfusional requirements and, consequently, a potential risk to develop iron overload. Iron transfusional loading is initially processed by macrophages after the breakdown of senescent erythrocytes and the iron released to plasma transferrin. This transfusional iron load can saturate the transferrin and result in the emergence of toxic "plasma nontransferrin bound iron" that is taken up by the parenchymal hepatic cells and stored as ferritin and hemosiderin. The iron can be reduced from ferric (Fe^{+3}) to ferrous (Fe^{2+}) ions and catalyzes the formation of free hydroxyl radicals (highly reactive) that may produce oxidative damage that may also affect lipids, proteins and DNA molecules and, finally, result in cellular death and/or fibrosis. Transferrin saturation index and serum ferritin serial measurements have shown to be simple and reliable techniques for efficiently evaluating iron overload and chelation therapy. The SQUID (Superconducting Quantum Interference Device) constitutes a noninvasive method for evaluating iron overload; however, this device is not available in Mexico and only five medical centers worldwide have this equipment. Magnetic resonance imaging (MRI) can be used to evaluate iron load in liver, heart, and pancreas and may replace invasive procedures such as heart or hepatic biopsies. Deferoxamine, deferiprone and deferasirox are currently used in the treatment of transfu-

Resumen

En pediatría, las anemias crónicas hereditarias, como la anemia drepanocítica y los síndromes talasémicos, y en menor grado la anemia aplásica, la aplasia pura de serie roja y los síndromes mielodisplásicos y diseritropoyéticos, cursan con requerimientos transfusionales elevados y consecuentemente, con el peligro potencial de desarrollar sobrecarga de hierro. El hierro de la sangre transfundida es procesado inicialmente por los macrófagos, que digieren los eritrocitos senescentes y retornan el hierro a la transferrina del plasma. Esta carga de hierro transfusional puede saturar la transferrina y llevar a la formación de "hierro no unido a transferrina" en el plasma; éste es tomado por las células del parénquima hepático y depositado como ferritina y hemosiderina. El hierro puede ser reducido de férrico (Fe^{+3}) a ferroso (Fe^{2+}), y en esta forma catalizar la formación de radicales hidroxilo (altamente reactivos), que pueden causar daño oxidativo y afectar lípidos, proteínas y moléculas de ADN y llevar a la muerte celular o fibrosis.

Diagnóstico. La medición del índice de saturación de la transferrina y las mediciones seriadas de ferritina sérica son métodos confiables y sencillos para evaluar la tendencia de la sobrecarga de hierro y la eficacia de la terapia de quelación. Un método no invasivo para esta evaluación es el Dispositivo de Interferencia Cuántica de Superconducción (SQUID). Este dispositivo no está disponible en nuestro país, y sólo cuentan con él cinco centros de todo el mundo. La resonancia magnética puede usarse para valorar la carga de hierro en el hígado, corazón y páncreas, y puede sustituir procedimientos invasivos como la biopsia cardiaca y hepática.

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sional iron overload. Deferoxamine is infused SC (20-40 mg/kg/day) in a continuous infusion connected to a portable pump for 10-12 h, 5x/week, mainly at night, and IV 20-40 mg/kg/day in a continuous infusion for 12-14 h. Intramuscular administration is not recommended due to the low chelation action. A daily dose of 75 mg/kg of deferiprone is recommended. Deferasirox is safe, orally administered and is as effective as deferoxamine. The effective oral dose is 20-40 mg/kg. Iron balance is obtained with 0.3 mg/kg/day urinary iron excretion in transfusion-dependent patients. Even though there is no conclusive evidence that all anemic polytransfused patients will develop iron overload, it is recommended to carry out integral surveillance programs to establish early iron chelation therapies.

Key words: anemia, transfusion, iron overload, chelation therapy.

Tratamiento. En la actualidad, la terapia de quelación de hierro se realiza con deferoxamina, deferiprona o deferasirox. Cuando la deferoxamina se administra por vía subcutánea se recomiendan 20-40 mg/kg/día en infusión continua de 10-12 horas, de preferencia nocturna, con bomba de infusión, durante 5 días a la semana, hasta lograr niveles de ferritina sérica ≤500 µg/L. Igualmente, para la vía intravenosa se utilizan de 20-40 mg/kg/día, administrados durante 12-14 horas en infusión continua. No se recomienda la administración intramuscular por su baja acción quelante. La dosis usual de deferiprona es de 75 mg/kg/día. El deferasirox en dosis de 20-40 mg/kg puede producir una tasa de excreción de hierro de 0.3 mg/kg/día, que permite mantener el equilibrio férrico en pacientes con transfusiones; posee una potencia comparable a la deferoxamina.

Aunque no existe evidencia categórica de que todos los pacientes anémicos politransfundidos desarrollarán sobrecarga de hierro, se recomienda realizar programas integrales de vigilancia para establecer un tratamiento temprano cuando se estime necesario.

Palabras clave. Anemia, tranfusión, sobrecarga de hierro, terapia de quelación.

Introduction

Anemic syndrome is part of a wide variety of disease entities. Iron deficiency is the most common cause of anemia in childhood, and treatment is constituted by orally administered iron salts. This iron is used by the body as required. Because the body has homeostatic mechanisms that regulate absorption of the metal, once the deficiency is corrected there is no danger of iron overload.

Other causes of anemia in childhood are genetic factors that produce qualitative and quantitative alterations in the synthesis of hemoglobin, entities that due to constant hemolysis have increased requirements for blood transfusion (BT) and, consequently, the potential danger of developing iron overload.

In this group of diseases we may mention sickle cell anemia and thalassemia syndromes. Less often we find conditions that may be congenital or acquired but during their evolution may have variable BT requirements depending on the response to the specific treatment.

This group includes all syndromes of marrow failure: acquired and congenital aplastic anemia, pure red cell aplasia (PRCA), myelodysplastic syndromes (MDS) and dyserythropoietic syndromes.[1] The progress made in recent decades in molecular biology research has allowed greater understanding of the pathophysiology of anemia, the mechanisms that occur along the pathological continuum that begin with these, treatment with BT therapy and, finally, iron overload as a pathological condition in addition to baseline disease and promotion of potentially fatal organ complications.

This complication, a result of the body's inability to remove accumulated iron, is largely avoidable. However, on many occasions, the care required by the disease prevents the clinician from sufficiently estimating the risk of iron overload. Currently, there are better orally administered chelating drugs that can eliminate this mineral without further exposing the pediatric patient to the deleterious effects of the iron.

Given the urgent need to reduce the incidence of iron overload as a high-risk contingency in patients with hematological disorders who require frequent BT, a group of hematologists from the Mexican Association for the Study of Hematology AC (AMEHAC) met to discuss concepts and updated recommendations that clinicians should consider in the treatment of this condition.

This paper summarizes the recommendations of this meeting as a contribution of the efforts of physicians interested in Mexican tertiary care centers.

Epidemiology of the anemias

History

In sickle cell anemia, genetic alterations of abnormal hemoglobin (hemoglobin S) are manifested when the patient is subjected to hypoxia, which induces red blood cells (RBCs) to change their structure and adopt a sickle (or scythe) shape. This new form causes its entrapment in the microcirculation, promotes lysis, and interferes in normal blood flow by obstructing smaller blood vessels, ensuring the formation of thrombi. Thalassemia syndromes are characterized by absence or reduced synthesis of á or â globin chains. As in sickle cell disease, clinical manifestations are observed from the first months of life, usually from the sixth month, at which time patients become dependent on BT. Furthermore, with this condition there exists an abnormally high absorption of iron in the intestine, which contributes to further increasing overload of this metal.[2] A publication from the National Institutes of Health of the U.S. reports that sickle cell anemia affects millions of people worldwide, mainly individuals from sub-Saharan Africa and those with the same genetic composition who now live in Spanish-speaking regions such as Mexico, the Caribbean region, and Central and South America. The same is true in Mediterranean countries close to Africa such as Greece, Italy, Turkey and even India.[2]

Abnormal hemoglobins, among which is included hemoglobin S, are very rare in Amerindians and, when found, are usually due to mixing with other ethnic groups. We have studied >3000 individuals from an aboriginal population,[3,4] and abnormal hemoglobins are virtually absent in Amerindians. The sporadic findings of hemoglobin S among this group are due to mixing with Africans brought as slaves during the Spanish domination. Similarly, â-thalassemia and sickle cell disease are rare genetic disorders in hospital populations, where frequencies ranging between 0.08[5] and 0.15% [3] for â-thalassemia and between 0.073 and 0.35%[5] for sickle cell disease, both heterozygous, are reported.

Studies in hybrid groups in selected areas of the country show that in some communities on the east and west coasts there are different frequencies of heterozygosity for hemoglobin S, and in some communities a high prevalence of hemoglobin S trait has been seen, similar to that observed in some areas of Africa. Three works exemplify this: the first study in a group of 200 subjects, inhabitants of a town located along the coast of the Gulf of Mexico (Veracruz) where 15% of the population were heterozygous for â-thalassemia and 6% also demonstrated sickle cell trait.[6] This paper posits the possibility that â-thalassemia was present in our country before the arrival of the Spanish in Mexico. In the second study, a group of Mexican individuals with African heritage showed a 12.8% frequency of heterozygosity for hemoglobin S, with a predominance of Bantu haplotype.[7] The third study was conducted in Mazatan, along the coast of Chiapas, Mexico, the municipality where at the beginning of the 19th century, 75% of the total population was mulato, reflecting the strong contribution of blacks in the genetic composition of the population. This study conducted at the National Autonomous University of Chiapas in 1991 showed that 15.3% of 300 subjects studied presented heterozygosity for hemoglobin S. This frequency is the highest reported in our country and reflects the behavior of this disease entity in other geographical areas, with the exception of the coast of the Gulf of Mexico

and the Pacific Ocean.[8] It is noteworthy that in Wintrobe's Book of Hematology[9] in the section for distribution of hemoglobin S in Mexico, it states that 1.2% of Mexicans (living in Texas) have this abnormality. This figure is based on a study by Killingsworth and Wallace[10] and possibly can be interpreted as being indicative of the mixture of American Indians or a mixture with blacks in that area. Although the prevalence of thalassemia syndromes in Mexico is not known in sufficient detail, it is thought that they are the most common hemoglobin abnormalities in selected populations of our country. In a community of individuals of Italian ancestry, a frequency of 1.3% for â-thalassemia heterozygotes was found.[3] Another prospective study that included 1639 blood samples obtained between 1987 and 2000 aimed at finding abnormally elevated levels of hemoglobin A2, and in 319 of these samples it was found, consistent with the diagnosis of â-thalassemia. This hemoglobin abnormality represented 74.2% of all abnormalities, both qualitative and quantitative, of the hemoglobin molecule.[11] Reyes-Nuñez et al. studied 500 consecutive individuals with or without anemia but with hypochromia and/or microcytosis and identified 48 cases (9.6%) with thalassemia: 37 with â-thalassemia and 11 with the á variety. These authors concluded that the thalassemia syndromes are not uncommon in Mexico, but often these cases are underdiagnosed and confused with iron deficiency anemia and, therefore, incorrectly treated with iron.[12] The first-line treatment in both cases involves frequent BT that help improve the quality of life but pose the risk of iron overload, which may generally affect the functioning of liver, heart and endocrine glands. Other disease entities seen in consultation and complicated by iron overload from transfusion therapy include PRCA characterized by anemia and reticulocytopenia resulting from an impaired production of erythroid precursors in the bone marrow, with normal leukocyte and platelet counts in peripheral blood. PRCA may be hereditary (Diamond-Blackfan anemia) or acquired. This is a rare disease in Mexico with 17 pediatric patients reported during a 22-year period at the Hospital Infantil de Mexico Federico Gomez (HIMFG), and 13 children in 13 years at the Hospital de Pediatria of the Centro Medico Nacional Siglo XXI of the Instituto Mexicano del Seguro Social (IMSS). Therefore, we can infer that in pediatric hospitals concentrated in the Federal District of Mexico there is a case of congenital PRCA per year.[13] The same is reported for aplastic anemia refractory to pharmacological management and with high transfusion requirements. In the IMSS affiliated population of Mexico City, Benítez-Aranda et al. reported an incidence of aplastic anemia in the pediatric population of 4.2 new cases/10^6 individuals/year.[14] Fanconi's aplastic anemia (FA) is the most common hereditary syndrome with a worldwide distribution affecting all races. At the Pediatric Hospital (Centro Medico Nacional Siglo XXI, IMSS) from 1989 until 2000, there were 75 children admitted, of whom 10 were characterized as having FA. Therefore, we can state that the ratio of acquired aplastic anemia vs. FA is 6:1.[15] MDS is rare in children and even when cases have been reported in infants from 2 months of age, its frequency is difficult to establish because they tend to be underdiagnosed. In Mexico there are insufficient data on the incidence in children. In contrast to that reported in the literature, in a review of 11 years in the National Pediatric Institute in Mexico, there were only 14 patients identified with diagnosis of new MDS: 43% were refractory anemia (RA), 21.5% RA with ringed sideroblasts (RARS), 28.5% RA with excess blasts (RAEB) and 7% RAEB in transformation (RAEB-t).[16] There are other conditions such as chronic renal insufficiency or oncological diseases that may present with iron overload caused by multiple BT.

However, in these two conditions the complication can be prevented: in the first case, the use of subcutaneous erythropoietin may improve anemia and eliminate the need for BT and thus the complication. In the second case, adequate control of the primary neoplasm is usually accompanied by he-

matologic recovery and rarely will require BT that may place the patient at risk for iron overload. Nevertheless, national information of diseases with iron overload condition is inadequate; hence, the relevance to conduct a multicenter study that allows us to establish the magnitude of the problem in our country.

All the previously mentioned hematological conditions will require at some point during their course chelation therapy to remove iron from the body. An iron-chelating agent binds to it and forms a chelate, which may be excreted, especially in the stool, correcting iron overload. Chelating agents and therapeutic phlebotomy have been used for a long time; however, ongoing research has brought new concepts and evidence for rational support of new and better drugs, criteria and resources all discussed in this paper. Its purpose is the dissemination of guidelines or useful recommendations for Mexican clinicians.

Diagnosis

Blood transfusion is a common treatment option used for patients with chronic anemia. Although there is no categorical evidence to determine that all polytransfused anemic patients will have overload of this mineral, comprehensive surveillance programs are recommended with the objective to establish early treatment, if deemed necessary.[17]

Iron in transfused blood is processed initially by macrophages, which digest senescent red cells and return the iron to plasma transferrin. This load of extrinsic transfusional iron can saturate the available transferrin and lead to the formation of iron unbound to transferrin in the plasma.

This form of iron is taken up rapidly by hepatic parenchymal cells through mechanisms that are independent of the transferrin-mediated uptake. Plasma nontransferrin bound iron is also formed by excessive ineffective erythropoiesis induced by erythropoietin. Excess iron in plasma is eventually taken up by cells and deposited in the form of histologically visible ferritin and hemosiderin. Most of the iron deposited in this manner accumulates in the liver.[18]

Iron can be reduced from ferric (Fe^{+3}) to ferrous (Fe^{2+}), allowing it to catalyze the formation of highly reactive hydroxyl radicals, which can cause oxidative damage and affect lipids, proteins and DNA molecules. Lipids probably play a primarily role on iron-mediated oxidative damage. The end result is the breakdown of lipid molecules with a concomitant effect on the integrity of the organelles that can lead to cell death. Another effect of the radicals is the increased production of TGF-â1, leading to increased synthesis of collagen and fibrosis. In short, iron-induced oxidative damage can cause cell death or fibrosis.[18]

Concentrated red cell transfusion in volumes e"120 mL/kg can cause iron overload that is correlated with serum ferritin levels 31000 μg/L. All patients with iron overload should be monitored in specialized centers where organ toxicity can be evaluated, in addition to providing health education to patients and general support. However in countries such as Mexico, a significant portion of the population does not have access to this follow-up.[17]

To establish the diagnosis of iron overload, it is necessary to determine the metal concentration in different organs and evaluate the function of the heart, liver and endocrine glands. The quantitative biochemical measurement of non-heme iron in liver biopsies is the most accurate method for assessing the magnitude of iron overload and to guide treatment. Although it cannot be considered a simple test, it is a safe and not very difficult procedure performed by experienced doctors (Table 1). The sample must be of adequate size (1 mg/g dry weight) and free of cirrhosis or focal liver lesions. Measurement is done by atomic absorption spectrometry performed by reference laboratories. In some programs, liver biopsies are recommended at the initiation of chelation therapy and every 2 years. The best indication to start chelation thera-

py is to obtain a non-heme iron concentration >7 mg/g dry liver weight.[18]

In indirect measurements, usually employing two or more parameters provides a good approximation of the total amount of iron accumulated. Serum iron is always high and transferrin saturation (fully saturated) correlates reasonably well with ferritin[19] (Figure 1). This is the main protein of intracellular iron storage and circulates in the plasma in small quantities. There is no known physiological function of secreted plasma ferritin, but it appears to have a logarithmic relationship with the body's iron reserves. Plasma ferritin, considered an acute phase reactant, and ascorbic acid deficiency, infection or acute or chronic inflammation and high concentration of erythropoietin may alter the relationship between serum ferritin and iron stores in the body.

The release of tissue ferritins can also be elevated, caused by damage to the liver or other tissues rich in ferritin, as well as due to liver dysfunction. Patients with sickle cell disease who receive frequent BT have a higher risk of presenting several conditions affecting the relationship of ferritin and iron stores, especially chronic and acute infections, inflammatory response to microvasculature infarctions, liver disease and chronic hemolytic anemia with erythroid hyperplasia. Nevertheless, serial measurements of serum ferritin remain a reliable and simple method to evaluate the tendency towards iron overload and effectiveness of chelation therapy.[20]

The soluble transferrin receptor (STfR) in plasma is derived from the total mass of cellular transferrin with 80% or more from the erythroid marrow. Although some reports indicate that the STfR concentration in plasma is decreased in iron overload, no quantitative relationship has been described between the magnitude of iron overload and STfR concentration.[20]

A noninvasive method for assessment of iron overload is the Superconducting Quantum Interference Device (SQUID). However, this device is not a resource available in our country, and currently is available in only five centers worldwide. Also, it should be taken into consideration that in some studies no correlation was found between the results obtained with SQUID, serum ferritin and liver iron concentration.[20]

The technique or pulse sequence that provides greater representativeness in the study of the musculoskeletal system is the T2* weighted image, so the MRI T2* can be used to assess iron load in the liver, heart and other organs such as the pancreas and thus replace invasive procedures such as heart and liver biopsy.[20] Functional evaluations of the myocardium can be done periodically, as myocardial iron overload is the most common cause of death from this condition.

Table 1. Evaluation of iron overload

Parameter	Normal	Iron overload		
		Light	Moderate	Severe
CHI (mg Fe/g dry weight)	<1.2	3-7	>7	>15
Serum ferritin (µg/L)	<300	1000-2500	1000-2500	>2500
Transferrin saturation (%)	20-50	>50	>50	>50
MRI T2* (msec)	<20	14-20	8-14	<8
ALT (U/L)	<250	>250	<250	<250
IUT (µM/L)	0-0.4	>0.4	>0.4	0.4

CHI, concentration of hepatic iron; MRI T2*, magnetic resonance image potentiated in T2*; IUT, iron unbound to transferrin; ALT, alanine transaminase.

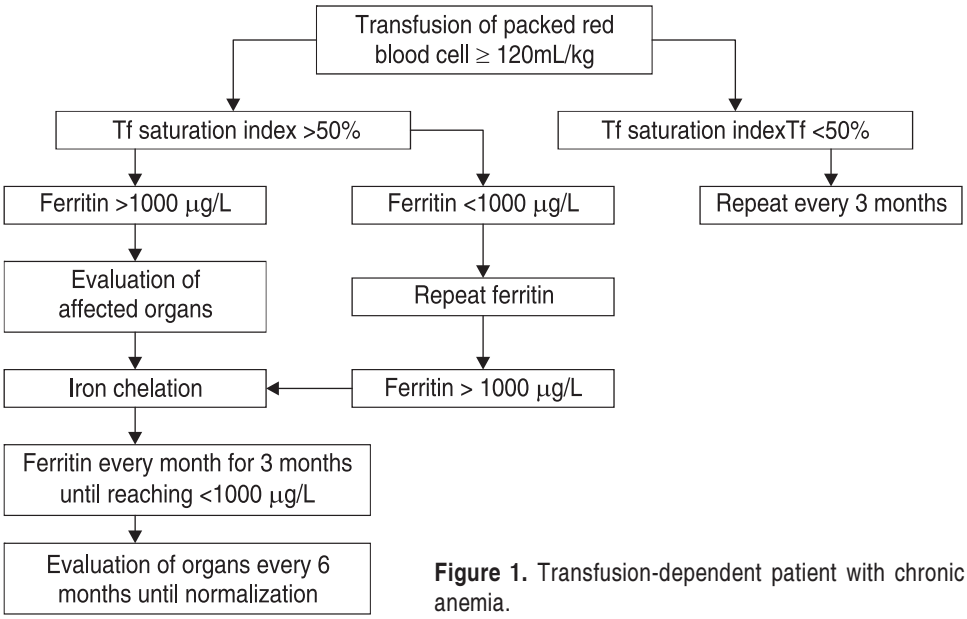

Figure 1. Transfusion-dependent patient with chronic anemia.

In Mexico as in other countries, T2* MRI devices are more common than the SQUID interface device and can be used in this population; however, it has been observed that the quantitation differs substantially according to the equipment used. This limits the comparability of measurements among various centers. Moreover, better MRI and CT imaging techniques are increasingly developed, although its use as a resource truly suitable for the detection of overload is not yet certified. We must also remember that these two diagnostic modalities are not economically accessible to a wide population.[18]

Treatment

Blood transfusion is a common option in the supportive treatment of the anemias previously mentioned. Once having identified a patient with high transfusion requirements, it is necessary to try to prevent iron overload, which is achieved through the recognition of the underlying disease and the institution of specific treatment. When iron overload is already installed, it is necessary to take measures to remove excess iron (Table 2).[21]

Deferoxamine

Trihydroxamic acid is produced naturally by *Streptomyces pilosus*, which has a high affinity for iron, to which it binds in a 1:1 ratio to form a hexadentated iron complex. Deferoxamine is poorly absorbed by the digestive tract and has a short half-life (20 min), so it should be parenterally administered. Its effectiveness in reducing organ damage induced by iron overload has been demonstrated since the 1970s using thalassemic patients as a model.

The results showed that administration for 52-83 months significantly reduced the risk of liver fibrosis due to accumulation of iron and also decreased the incidence of cardiac insufficiency to reverse the associated clinical pictures such as arrhythmia.

For the SC route of administration, a 20-40 mg/kg/day continuous infusion for 10-12 h is recommended, preferably at night, with infusion pump for 5 days a week to obtain ferritin levels d"500 mg/L. Similarly, for the IV route, 20-40 mg/kg/day is recommended, dissolved in 1000 mL of 5% dextrose

solution and administered during 12-14 h continuous infusion. Because it requires hospitalization, 1-2 days each 3-4 weeks is recommended along with the following indications: rapidly decrease the iron overload prior to hematopoietic stem cell transplantation, after the transfusion of packed red cells and before the onset of oral chelation. Intramuscular administration is not recommended due to its low chelating action.

As collateral side effects, local reactions may occur at the application site as well as affecting sight, hearing and bone. There are reports of acute pulmonary toxicity with hypoxemia and interstitial fibrosis in patients who have been treated long term with high doses of this chelating agent.

Deferiprone

Deferiprone was the first oral chelator to be developed. It is a bidentate chelator in which three of its molecules unite for every molecule of iron. It is absorbed rapidly and reaches peak concentrations in 45-60 min. Its plasma half-life was estimated at 91.1 min,[22] and it is inactivated in the liver by glucouridation, which induces iron excretion in the urine almost exclusively and only a small part in feces. The usual dose is 75 mg/kg/day.[23]

There are few studies comparing deferiprone with deferoxamine. In a multicentric, prospective, and randomized trial, 144 thalassemic patients with baseline serum ferritin of up to 3000 mg/L received deferiprone at 75 mg/kg/day in three doses, or deferoxamine at doses of 50 mg kg/day SC over 12 h, 5 days/week for 1 year.[24] There were no significant differences recorded in the average reduction rate of serum ferritin: 222 mg/L and 232 mg/L for deferiprone and deferoxamine, respectively. Finally, it is also reported that deferoxamine is inferior to deferiprone in cardiovascular protection.[25]

The most common adverse effects of deferiprone consist of color changes in urine and gastrointestinal discomfort (nausea, vomiting, abdominal pain) that is usually manageable. Agranulocytosis is the most severe adverse effect, but the mechanism that triggers it is unknown. Its incidence is low and it responds to treatment discontinuation. In some patients deferiprone has been used in combination with deferoxamine, but it is not available in Mexico.

Deferasirox

Deferasirox is the most recently developed binder, designed with a molecular model that is part of the bi-hydroxy-phenyl-triazole family. It binds to iron in a 2:1 ratio, is rapidly absorbed, reaches peak plas-

Table 2. Properties of the chelating agents[21]

Property	Deferoxamine	Deferiprone	Deferasirox
Chelating with Fe	Hexadentate (1:1)	Bidentate (3:1)	Tridentate (2:1)
Usual dose	25-40 mg/kg/day	75 mg/kg/day	10-40 mg/kg/day
Route of administration	SC, IV	Oral	Oral
Excretion	Urinary, fecal	Urinary	Fecal
Adverse effects	Local reactions, ophthalmic, auditory, bone, lungs, allergies and neurological	GI disturbances, agranulocytosis/ neutropenia, arthralgia, elevation of transaminases	GI disturbances, rash
Status	Approved	Approved in Europe for patients refractory to deferoxamine	Approved

Table 3. Guidelines for administration and follow-up of iron-chelating agents[27]

	Deferoxamine	Deferiprone	Deferasirox
Characteristics Half-life 20 min	IV and SC administration Excretion: urine Excretion: urine faces Dose: 20-60 mg/kg/day	Oral administration Half-life 2-3 h Excretion:feces Dose: 50-100 mg/day	Oral administration Half-life: 8-16 h Dose: 20-30 mg/kg/day
Monitoring guidelines	Annual audiometry and ophthalmalogic exam Trimestral serum ferritin Annual hepatic Fe Annual cardiac Fe after 10 years of age	Weekly blood panel with differential ALT monthly for 6 months, afterwards every 6 months Serum ferritin trimonthly Liver Fe annually Cardiac Fe annually after 10 years of age	Monthly serum creatinine, Monthly ALT Monthly serum ferritin Annual Fe levels Annual cardiac Fe after 10 years of age
Advantages	Long-term experience Effective in maintaining normal or near normal iron deposits Reverse cardiac disease with intensive therapy Can be combined with deferiprone	Oral activity Higher removal of cardiac Fe Can be combined with deferoxine Well-established safety profile	Oral actividad once daily Equivalent with deferoxamine at higher dosage Studies in different hematologic diseases
Disadvantages	Requires parenteral infusion Toxicity to eyes, ears and bones Poor attachment	Unable to obtain negative balance with doses of 75 mg/k/day Risk of agranulocytosis and need for weekly blood panel	Limited long-term data Necessity for renal monitoring Unable to obtain negative balance with high recommended doses

ma levels in 1-3 h, is highly selective for this element, does not affect zinc and copper levels,[26] and the excretion of iron is through feces. Its plasma half-life is 11-19 h and it can be extended using high doses. It has been shown that doses of 20-40 mg/kg can achieve a rate of iron excretion of 0.3 mg/kg/day, which may be sufficient to maintain iron balance in patients on BT therapy.[26]

This drug has a potency comparable to deferoxamine and is safe and easily administered orally. For best absorption it should be taken 30 min before breakfast. It can be dissolved in apple or orange juice and should not be mixed with metal utensils. Among the adverse effects were headache, rash, and GI discomfort including nausea, vomiting and abdominal pain, rarely requiring dose adjustment. Its use requires regular monitoring of renal and hepatic function and ophthalmological and auditory assessment with annual evoked potentials (Table 3).

It is important to identify high requirements of BT in the patient when iron overload is present and initiate timely chelation therapy. Subsequently, strict control and monitoring of treatment response is necessary, along with identification of the undesirable effects of chelating drugs and the time in which these should be discontinued when serum ferritin levels are <500 mg/L.

The patient who has reached iron equilibrium but requires continuation with periodic administration of concentrated erythrocytes should have quarterly serum ferritin monitoring and evaluation of the use

of iron chelators if transfusion requirements are e"120 mL/kg/day.[27]

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