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INCIDENCE AND PREVALENCE OF CHRONIC IRON POISONING AND IT'S MANAGEMENT: A REVIEW

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ABSTRACT

Iron, an essential nutrient causes serious diseases in deficient state. But more serious events occur due to the toxicity of iron overload and this leads to morbidity and mortality of a significant population of the world. Chronic iron poisoning can occur due to daily high dietary iron intake, chronic liver disease, rare genetic disorders of iron metabolism, etc. But the commonest causes of severe iron overload are Hereditary Haemochromatosis, Massive ineffective erythropoiesis, secondary iron overload due to frequent repeated red cell transfusion in congenital anaemias (e.g. β-Thlassaemia, Sickle cell anaemia) and Acquired refractory anaemias (e.g. myelodysplasia, aplastic anaemia). In India and South -East Asia, prevalence of Thalassaemia and Sickle cell anemia is indeed alarming. Though, iron poisoning has been a health concern for quite a long period of time, only three drugs could have been developed and put into practice. Even in 2014, not a single agent fulfils the requisites of an ideal iron chelator. Desferrioxamine, Deferiprone and Deferasirox are used as a single drug or in combinations in cases of iron overload diseases and has shown indeed promising results by decreasing the morbidity and adding quality years to life of patients undergoing frequent red cell transfusions. However we still wait for an ideal iron chelator as few drugs are already into phase II clinical trials.

KEYWORDS: Iron, Iron toxicity, Desferrioxamine, Deferiprone, Deferasirox

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INTRODUCTION

Iron, the most abundant trace mineral is the 26th element of the Periodic table. Iron is an essential nutrient which is required as: haemoglobin in red blood cells for transporting oxygen from lungs to the tissues; in the form of myoglobin for storage and use of oxygen in muscles; and a component of a number of enzymes which are essential for many metabolic and synthetic functions. Iron is found in minerals hematite, magnetite and siderite [1] in earth's crust. Iron is not only an environmental toxin [2] but is even toxic to human body in excess as it promotes free radical reactions. In biological systems iron is commonly found in three oxidative states: Fe(II), Fe(III) and to a lesser extent Fe(IV). Excessive iron accumulation may eventually lead to tissue damage. Severe iron overload, arbitrarily defined as an excess of more than 5gm is confined to genetic haemochromatosis and iron loading anaemias due to chronic blood transfusions. Chronic iron overload result in significant morbidity and mortality worldwide. Among the causes of Chronic iron poisoning, the most notorious ones in India and South East Asia are due to: (1) Excess iron absorption as in Massive Ineffective Erythropoiesis (e.g. β-Thalassaemia Intermedia, Sideroblastic anaemia) and (2) Repeated red cell transfusions as in Congenital anaemias (e.g. β-Thalassaemia Major, Sickle cell anaemia). Management of Chronic iron poisoning has drastically changed from early 1960s when Desferrioxamine(DFO) was introduced. There after oral iron chelators as monotherapy or in combination therapy has not only enhanced the life span but also gifted a better quality of life to patients with haemosiderosis.

IRON: A BIOCHEMICAL APPROACH; FROM NUTRIENT TO TOXIN

The normal human body contains approximately 3-4gms of iron. The majority of body iron (~60-70%) is utilized within haemoglobin in circulating red cells [3]. Approx. 20-30% of body iron is stored in hepatocytes and reticulo-endothelial macrophages, to a larger extent within ferritin and has degradation product haemosiderin. Dietary iron exists in (a) Haem form (found in meat) and (b) Non-haem form (in cereals, vegetables, eggs etc). Calcium, phytates and phenolic compounds in tea decreases availability of iron for absorption. On the other hand, Meat and Vitamin C (ascorbic acid) increases the mucosal intake of iron. Daily duodenal absorption [4] of iron from diet ranges from 1-2 mg. The low pH of the gastric effluent dissolves ingested inorganic iron and facilitates its enzymatic reduction to ferrous form (Fe II) by brush boarder ferrireductase Dcytb[5]. It is then transported into the enterocytes by DMT1. This iron is either stored by the enterocytes (ferritin) or transferred across basolateral membrane to plasma transferring, which is mediated by ferroportin 1 [6] or also known as MTP1[7].

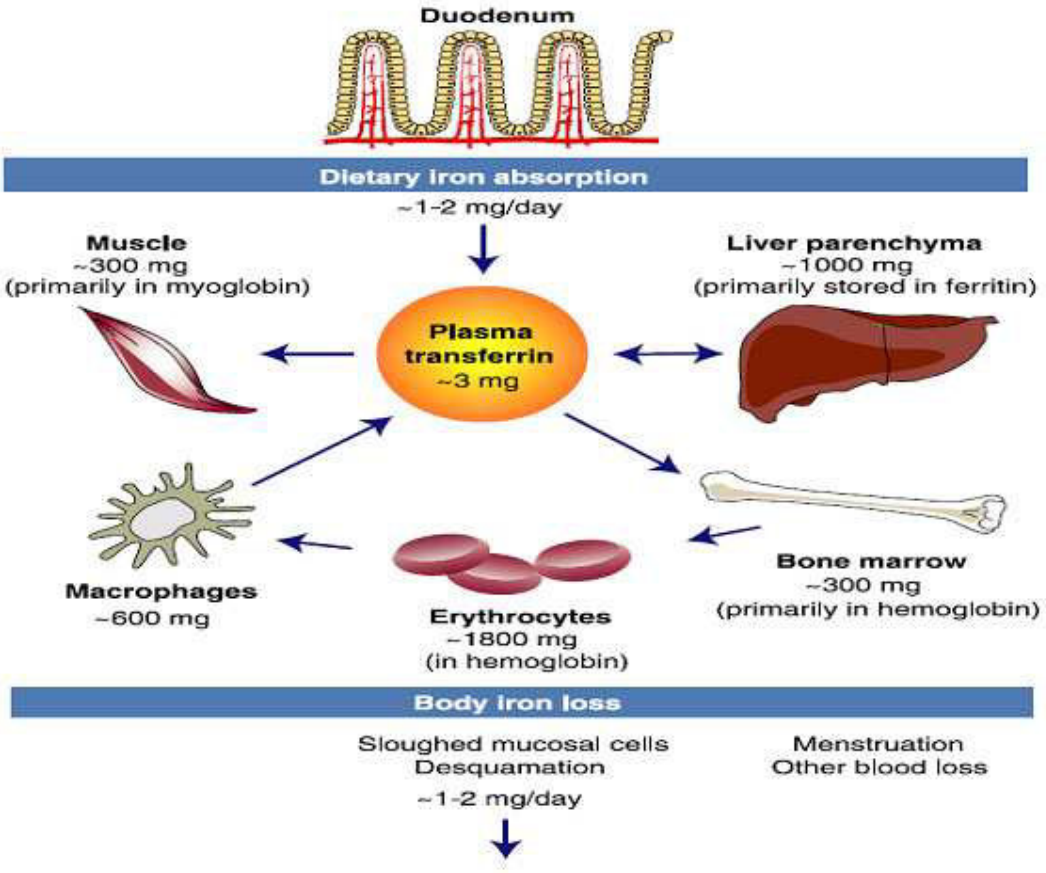

Figure 1
IRON DISTRIBUTION IN ADULT HUMAN BODY

The hephastin oxidizes Fe(II) to Fe(III) and this Fe(III) gets bound to circulating transferring and passes through portal system of liver. Hepatocytes , known to be the major site of iron storage take up transferring bound iron via TfR1 (Transferrin receptor) and TfR2 (homologus protein). Iron is mostly utilized in bone marrow for Haem synthesis. Iron has no specific mechanism of excretion, and so iron homeostasis is controlled by matching the intestinal uptake and transfer of iron to the amount needed to replace adventitious losses (varies from 1-4mg through blood loss, menstrual bleed, desquamation of skin) of iron and the amount needed for growth and reproduction. Iron toxicity is related to the generation of free radicals [2, 8] resulting in damage of cell components in certain chronic diseases. Studies reveal that inflammation and acute phase response interact with iron metabolism [9].

$$O_2^- + Fe^{3+} \rightarrow O_2 + Fe^{2+}$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO\cdot + OH^- \quad \{\text{Fenton Reaction}\}$$

Net Reaction

$$O_2^- + H_2O_2 \rightarrow O_2 + HO\cdot \text{ (hydroxyl radical)} + OH^- \quad \{\text{Haber Weiss}\}$$

Figure 2
Iron-catalyzed generation of the hydroxyl radical via the Fenton reaction; the net Haber–Weiss reaction is also indicated.

O_2^- releases the stored iron from ferritin. The free iron reacts with O_2^- and H_2O_2 to produce more reactive and toxic free radicals such as hydroxyl radical [$HO^\cdot$]. This [$HO^\cdot$] radical can depolymerise polysaccharides and cause break in DNA strands, inactivate enzymes and initiates lipid per oxidation [2,10] leading to cell death.

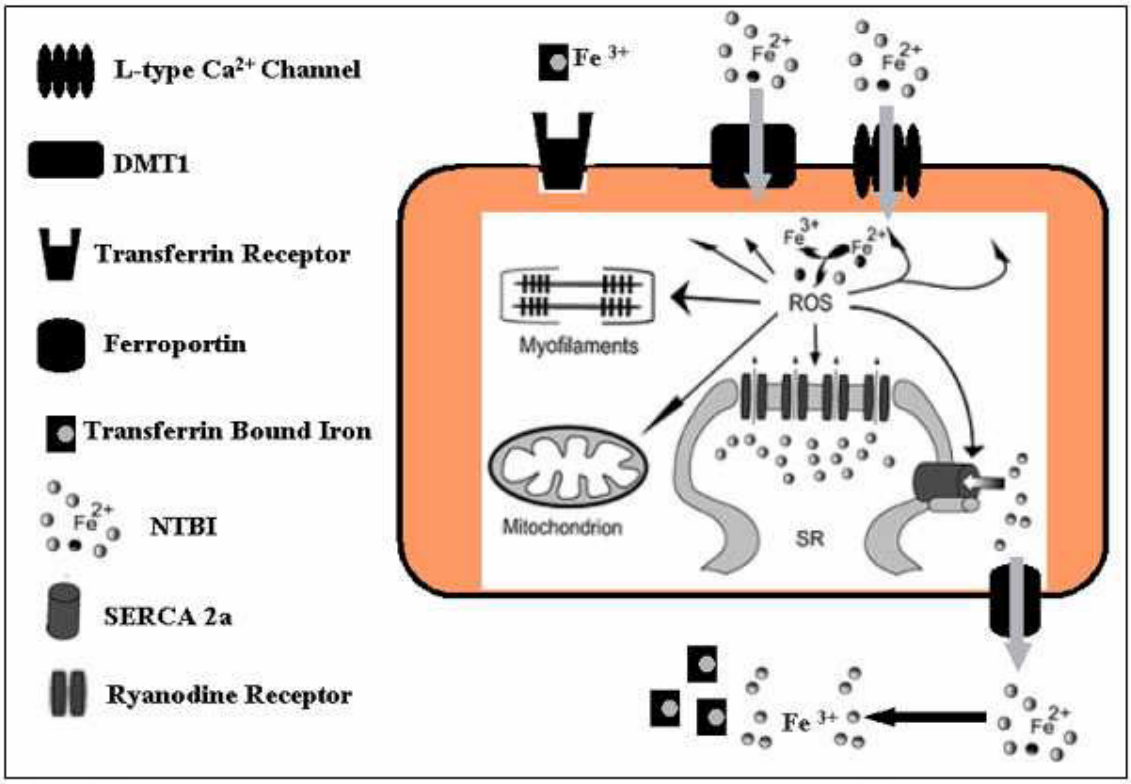

Figure-3
Cellular iron transporters and the redox cycling of iron within cell.

IRON OVERLOAD

Incidence and Prevalence

20mg/kg or more of elemental iron will lead to iron toxicity. However lethal outcomes have been reported at levels greater than 60mg/kg. Iron overload may occur in acute condition due to increased iron intake through overdosed intake of oral or parenteral iron preparations. This leads to acute iron poisoning which is more prevalent in children younger than 6 years. Death has also been reported after ingestion of as few as 5 pills in a child below 3 years. Chronic iron poisoning is a term used for gradual increase in serum iron and serum ferritin level due to high dietary iron intake or some underlying conditions which may be (1) Genetic Haemochromatosis, (2) Massive Ineffective Erythropoiesis as in β-Thalassaemia Intermedia, Sideroblastic Anaemia, Congenital Dyserythropoietic Anaemia, (3) Congenital Anaemias where repeated blood tansfusions required like β-Thalassaemia Major, Sickle Anaemia, Red Cell Aplasia and (4) Acquired Refractory Anaemias like Myelodysplasia, Aplastic Anaemia.

GENETIC HAEMOCHROMATOSIS

Also called Hereditary Haemochromatosis (HH) is an autosomal recessive disorder is now classified according to the genetic defect causing iron overload. Vast majority of cases are Type 1, involving HFE gene, and accounts for the most common genetic condition in N.European population. In UK, about one in eight people are carriers of C282Y mutation of HFE gene and 1 in 200 is homozygous for this mutation. However, it also occurs in African and Asian population at very low gene frequency. In this genetically heterogeneous

disorder due to deficient hepcidin production, high absorption of dietary iron from intestine eventually leads to mucosal iron transfer to plasma. Type 2 Haemochromatosis also known as Juvenile haemochromatosis usually leads to severe iron accumulation and becomes symptomatic before the age of 3 years [11].This occurs due to either haemojuvelin mutations or mutations in Hepcidin (HAMP) gene. Type 3 Haemochromatosis occurs due to mutations in the gene for Transferrin receptor (TfR2). Type 4 Haemochromatosis also known as ferroportin disease is inherited as autosomal dominant trait and is due to heterogeneous mis-sense mutations in gene for iron exporter ferroportin.

IRON LOADING ANAEMIAS: Main Cause of Secondary Iron Overload.

The incidence of Thalassemia and sickle cell anaemia in India and South-East Asia is quite high. Even after the awareness programmes and pre-marriage screening programmes; a significant new number of cases are being identified with these genetic disorders. The basic treatment for the first disease, i.e., Repeated Blood transfusions leads to a more serious second disease known as Iron Overload. Each millilitre of red cells transfused adds up to 1mg of iron to the recipient.

Iron Content in each transfusion= Volume(ml) x Haematocrit x 1.16 mg

On the other hand, ineffective erythropoiesis that occurs in β-Thalassaemia major, sideroblastic anaemia and congenital dyserythropoietic anaemias lead to increased iron absorption from gastro-intestinal tract. Thalassaemia major is the most common genetic disorder associated with secondary iron overload. Early and severe iron loading occurs in Thalassaemia major patients due to (1) ineffective erythropoiesis, (2) Rapid haemolysis and (3) gastrointestinal iron hyper absorption.

TABLE 1
Peak Serum Iron in Correlation with Toxicity

Peak serum iron (µg/dL)	Toxicity
50-150	Normal Range
150-300	Mild
300-500	Moderate (rarely develop serious complications)
>500	Severe (serious systemic toxicity)
>1000	Significant morbidity and mortality

Data extacted from: Liebelt LL and Kronfol R; Velez LI and Delaney KA.

COMMON TOXIC EFFECTS OF IRON OVERLOAD

GROWTH FAILURE

It occurs during the first decade of life in iron overloaded patients. Defect in synthesis of insulin like growth factor (IGF1) [12-14] in liver, resistance of growth hormone and dysfunction of thyroid occurs, leading to growth failure.

GONADAL FAILURE AND DELAYED PUBERTY

Gonadal failure due to iron overloading of anterior pituitary results in testicular atrophy in males and amenorrhoea in females. Hypogonadism [15-18] leads to impaird glucose tolerance, hypoparathyroidism and delayed puberty in second decade of life.

LIVER TOXICITY

Iron accumulation in hepatic parenchymal cells has been documented even after only 2 years of repeated transfusion therapy [19]. The elevation of liver enzymes i.e. SGPT & SGOT is the earliest manifestation of hepatic iron toxicity. Cirrhosis of liver and hepatocellular carcinoma may occur following portal fibrosis.

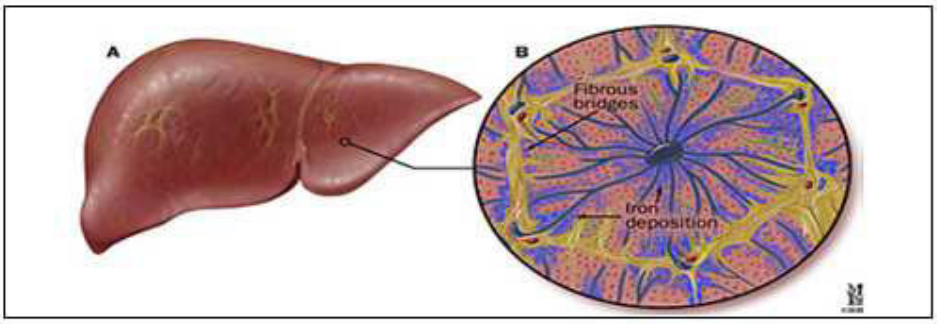

Figure-4
(A)Iron deposition in liver (B)Histological view of iron overload and fibrotic changes.

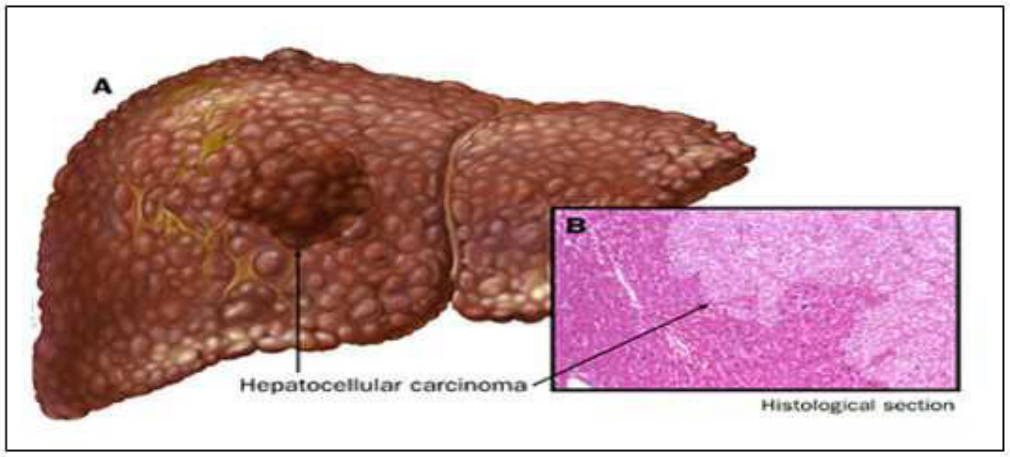

Figure-5
(A) Hepatocellular Carcinoma in Cirrhotic Liver. (B) Corresponding Histological section.

CARDIAC TOXICITY

Transfusional iron overload leads to the deposition of iron in myocytes and interstitial fibrosis develops. Signs and symptoms of Congestive cardiac failure appears by the mid teen [20]. Small amount of unbound iron has the ability to generate reactive oxygen metabolites leading to toxicity. Chronic pulmonary hypertension [21], myocarditis [22], arterial fibrillation, supraventricular tachycardia or conduction defect may result due to cardiac fibrosis following iron overload.

OTHER MANIFESTATIONS OF IRON TOXICITY

A. DIABETES due to deposition of iron in β cells of pancreas leading to dysfunction of islet cells and leading to insulin deficiency.
B. ARTHROPATHY of iron overload involves both large and small joints and individual bones. Cartilage loss, osteoporosis, demineralisation, osteoporosis, cyst formation are the prominent X-Ray findings that are found in patients with iron overload in their 2nd to 3rd decade of their life.
C. Iron induced oxidative stress combined with defective antioxidant capacities promotes neuronal death and neurodegeneration and may result in diseases like Parkinsonism and Alzheimer's disease.
D. Cancer and iron toxicity, though not directly related, but malignant transformation [23] may occur due to chronic replicated oxidative stress. Hepatocellular carcinoma has been illustrated as a common complication of hereditary haemochromatosis [24].

MONITORING FOR BODY IRON BURDEN INDIRECT ASSESSMENT

1) LABORATORY TESTS

(a) *Serum Ferritin*: The serum ferritin though imprecise is an indirect measure of total iron overload in tissues. Serum ferritin higher than 1000µg/L (Normal- 40-340µg/L in males and

14-150µg/L in females) is endangered for iron induced organ damage.

(b)Liver function tests: Increased levels of Liver enzymes (SGPT, SGOT and Bilirubin) are indirect market of hepatic cellular damage in an underlying high serum ferritin.

***(c)Hormonal evaluation*:** Diabetes-Fasting Blood sugar, Glucose Tolerance Test;

Growth & sexual development – GnRH realease, Testosterone, Estradiol, Leutinizing hormone, Follicular stimulating hormone levels; Thyroid- T_4, TSH; Parathyroid- Calcium, Phosphate, PTH level.

2) OTHER METHODS OF DIAGNOSING ORGAN DAMAGE:

(a) Cardiac Evaluation

i) ECG, ECHO, Doppler Echocardiogram are few tests that analyse the cardiac function but are not sufficiently sensitive for early detection of iron induced cardiac dysfunction [25-29].

ii) T_2^* MRI scan of heart is the latest, non invasive and sensitive method of assessing cardiac iron of individual patients.

(b) Hepatic evaluation

T_2^* MRI (Ferriscan) Estimation of liver iron surpassed other non-invasive methods like Computered Topography, Nuclear Resonance Scattering from Manganese 56 and Superconducting Quantum Interference Device(SQUID) in terms of availability and approach. The T_2^* MRI scan has become the new gold standard for measuring liver and cardiac iron and can assess iron content rapidly and iron levels can be quantified reproducibly. The lower the T_2^* value, the higher is the LIC(liver iron concentration). However, the correlation between MRI derived myocardial iron and liver iron still remains inappropriate.

(c) Bone

Bone Mineral Density(Dexa Scan) has been cited for detection of early osteopenia and osteoporosis in iron overloaded patients. On the other hand Plain digital X-ray of Joints may reveal the bone age and also the structural changes can be analysed.

DIRECT ASSESSMENT

(1) LIC from Liver Biopsy

Measurement of LIC can be done by chemical determination on a liver biopsy sample.This invasive procedure is still the gold standard measure for measuring iron concentration of liver and also can predict total body iron stores, by formula:

Total body iron stores(mg/kg)= 10.6 x LIC (in mg/g dry wt).

Levels of 7-15 mg/g dry weight indicates liver damage; however normal is upto 1.8mg/g dry wt.

(2) Marrow Iron Studies

This is also an invasive procedure, with decreasing popularity and acceptance. High marrow iron stores occur in patients receiving repeated blood transfusions due to underlying haematopoietic disorders.

TREATMENT OF CHRONIC IRON POISONS

Early detection and aggressive iron unloading are the basic requirements in case of efficient therapy of chronic iron poisons. A high ferritin above 1000 µg/L(10g) in a case of hereditary haemochromatosis or in a patient receiving repeated blood transfusions as in Thalassemia Major and Sickle Cell disease requires maximum therapy.

A. PHLEBOTOMY

Phlebotomy which is indicated mainly in Hereditary Haemochromators, must be initiated when serum ferritin rises above 200mcg/L). 500 mLof blood which typically contains 200-250 mg of Iron is removed weekly until ferritin falls in deficient range. For maintenance, men will require 3-4 sessions a year and women 1-2 sessions per year. For every 5 phlebotomies, 1 gm of excess iron is generally removed. In these patients, serum ferritin even if being reduced to below 40-50 µg/L; it is found to have markedly improve symptoms of weakness, lethargy, abdominal pain & lowering of serum aminotransferases.

Figure 6
Phlebotomy Technique.

B. IRON CHELATION THERAPY

Initiation of iron chelating therapy, in practice, by most clinicians is relied upon the serum ferritin level. As this practice can lead to inaccurate assessment of iron burden, emphasis must be given on measurement of liver iron of ultrasound guided liver sample; after 1 year of regular transfusion.

There are basically three iron chelating agents marketed:

1. Desferrioxamine mesylate(DFO) – It is a parenteral preparation that was introduced in 1960's. It is the first iron chelator.
2. Deferiprone(DFP) – It is the first oral iron chelator that has been initially introduced in 1980 in Europe and is being used since 1994 in India.
3. Deferasirox(DFX) – It is the newest, rationally designed oral iron chelator and is being marketed from 2005.

DESFERRIOXAMINE MESYLATE (DFO, Deferoxamine)

Desferrioxamine mesylate (Desferal®, Novartis) is a 50 year old drug and has been the gold standard iron chelating agent recommended not only in chronic iron poisoning but also in acute iron poisoning.

Source

It is prepared from trihydroxamic acid produced by Streptomyces pilosus.

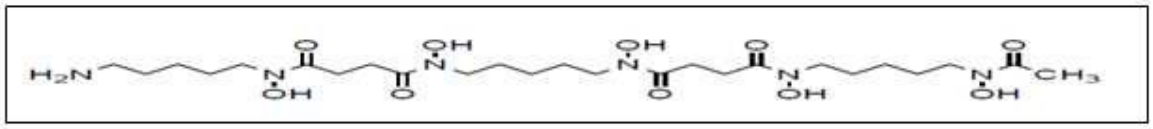

Figure 7
DESFERRIOXAMINE [Hexadentate(1:1) High MW]

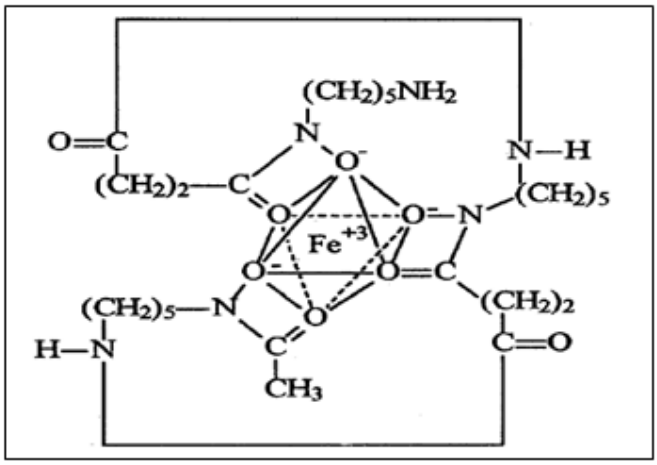

Figure 8

Octahedral structure of ferrioxamine complex. (Source: Goldfrank LR, Flomenbaum NE, Lewin NA, Weisman RS, Howland MA, Hoffman RS, editors. Goldfrank's toxicologic emergencies. 6th ed. Stamford: Appleton & Lange; 1998. p. 628).

Pharmacokinetics

Desferrioxamine, a straight chain molecule with high molecular weight, is not absorbed orally. The parenteral injection of DFO is rapidly cleared from plasma, taken up by hepatocytes or metabolized in tissues, excreted in bile and reabsorbed by intestine. At physiological pH, DFO complexes with ferric ions. [30]. It chelates only free iron and has no effect on iron of haemoglobin, myoglobin, haemosiderin or ferritin. DFO has high binding constant for Iron (10^{31}) & the straight chain hexadentate molecule fold around a single atom of iron to form a stable octahedral complex. 100 mg desferrioxamine can bind to about 9 mg of iron and gets excreted in urine & stool in the form of red chelates, Ferrioxamine. DFO has a short half life and V_d is 0.6- 1.2L/kg. Vitamin C (in a dose of 2mg/kg) if given prior to DFO infusion increases iron excretion by increasing the availability of chelatable iron. Standard adult dose is 40mg/Kg given as a 8-12 hour infusion via subcutaneous route on at least 5 days each week delivered with portable pump [31, 32]. Intravenous desferrioxamine infusion during blood transfusion is also in practices. Intermittent IV DFO infusion has also shown good results in decreasing liver iron concentration. Desferrioxamine has been efficacious in significantly decreasing body iron burdens and reversing hepatic iron overload. DFO is not introduced at a very young age & the dose is reduced as iron loading falls. Desferrioxamine is reported to be an animal teratogen but in experiments, it has shown little transfer across placenta [33]. Desferrioxamine has shown no adverse effects in post transfusion iron overloaded pregnant thalassaemia major patients [34-37].

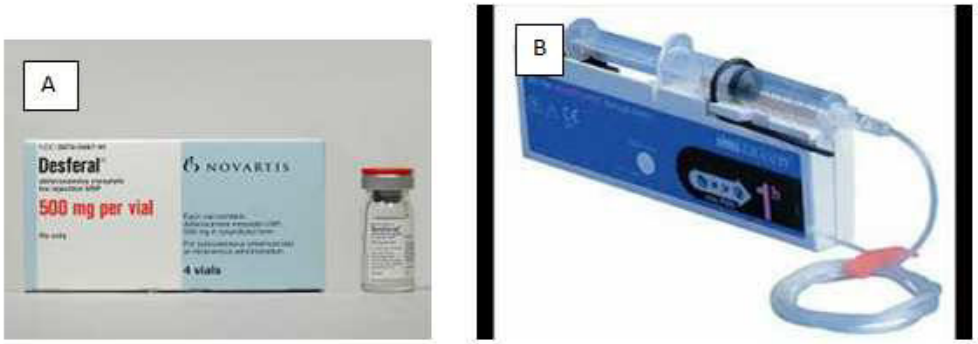

Figure 9

(A) Desferal® Vial as marketed in India. (B) Infusion pump.

Side Effects

i. Local soreness at site of injection occurs due to needle being inserted too superficially.
ii. Auditory neurotoxicity in the form of high tone sensorineural hearing loss.
iii. Visual neurotoxicity resulting in loss of visual field, retinal pigmentation.
iv. There is a high risk of Yersinia enterocollitis in iron overloaded patients on DFO therapy.

Therapeutic Index (TI)

$$\frac{\text{Mean Daily Dose (mg/kg)}}{\text{Current Serum Ferritin (µg/c)}}$$

TI if below 0.025, does not cause auditory or visual side effects.

DEFERIPRONE (1,2 – dimethyl 1-3-hydroxypyrid-4-one)

Deferiprone (Ferriprox®,Kelfer®,Cipla) is the first oral active Iron chelator that was first introduced in 1980. It is a bidentate chelator and is a member of hydroxypyridin-4-one[38].

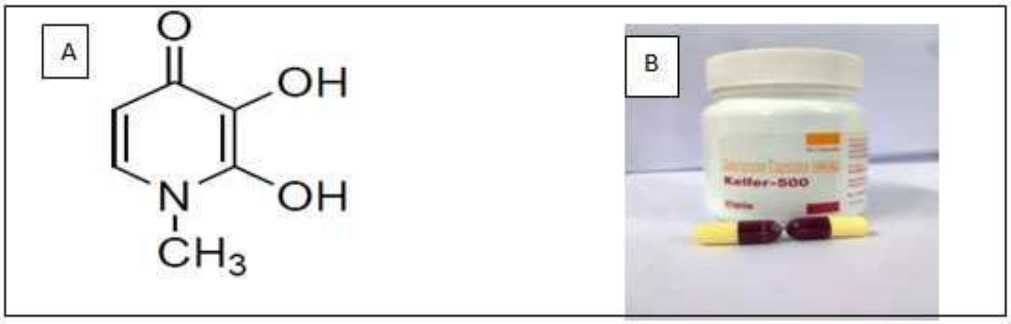

Figure 10
(A)DEFERIPRONE [Bidentate (3:1) Low MW]; (B) Kelfer® as marketed in India.

Pharmacokinetics

It has low MW (1/3rd of the MW of DFO), neutral charge, relative lipophilicity and these accounts for the rapid absorption from gut. It appears in plasma within 5-10 mins of ingestion (peak conc- 1 hour). Deferiprone requires three molecules fully to bind iron(III) , each molecules providing two co-ordination sites. Deferiprone mobilizes iron from parenchymal and reticulo-endothelial pools & from transferrin, ferritin and haemosiderin and forms chelator iron complex which is excreted with free drug and glucoronide derivative in urine[39].

Dosage

Minimum of 75 ml/kg/day – orally in form of 500 or 250 mg capsules in evenly divided doses. Deferiprone has been studied to cross Blood Brain Barrier and it has shown benefits in treating neurological conditions assosciated with iron loading in brain. Deferiprone has been efficacious in chelating cardiac iron overload . Few uneventful pregnancies undergoing Deferiprone therapy has been reported with healthy newborns.

Side Effects

- Cytopenia, Agranulocytosis, mainly Neutropenia.
- Musculoskeletal pain and athralgia, swelling of joints.
- Gastric intolerance.

It has been noticed that patients with lower initial ferritin levels had shown less dramatic decrease of ferritin level.

DEFERASIROX (ICL 670, Exjade®, Asunra®)

After a long wait, another oral iron chelator came into being after rigorous scientific scrutiny. Deferasirox, a Tridentate (2:1)

molecule with low MW. It is an N-substituted bes-hydroxyphenyl-triazole [40] which has high iron binding potency and selectivity [41]. One ferric iron gets bounded by 2 molecules of chelator to form a complete complex, which is cleared by the liver & excreted through bile. Deferasirox has shown 5 times more potency than DFO & 10 times more potency than Deferiprone [42]. Recent data regarding deferasirox's ability to treat cardiac iron overload in initial human studies are promising. Researchers have found that deferasirox is effective in decreasing cardiac iron burden; however, the results regarding if it is effective in removing cardiac iron in cases of severe iron overload are conflicting[43-45].

Pharmacokinetics

The single daily dose ranges from 20-30 mg/kg and sometimes upto 40 mg/kg. It is given early morning before breakfast after dissolving it in water or fruit juice. Deferasirox has a bioavailability of 70%. The elimination half life is 11-18 hrs [46]. Deferasirox has substantially shown a significant plasma level even after 24 hours of oral intake. Metabolism occurs predominantly by glucoronidation in liver. Deferasirox has also shown a promising result in preventing cardiac iron accumulation [47]. In case of liver iron concentration; Deferasirox at dose of 10-30 mg/kg/day was equivalent to Desferrioxamine in lowering hepatic iron overload[48]. At the conclusion of the study of 1,774 iron overloaded patients, 51% of patient were receiving greater than 30 mg/kg/day and 39.6% were receiving between 20-30 mg/kg/day. There was a statistically significant reduction in serum ferritin from baseline[49]. Although a majority of deferasirox studies have enrolled thalassemia patients, it has shown efficacy in treatment of other conditions associated with iron overload.

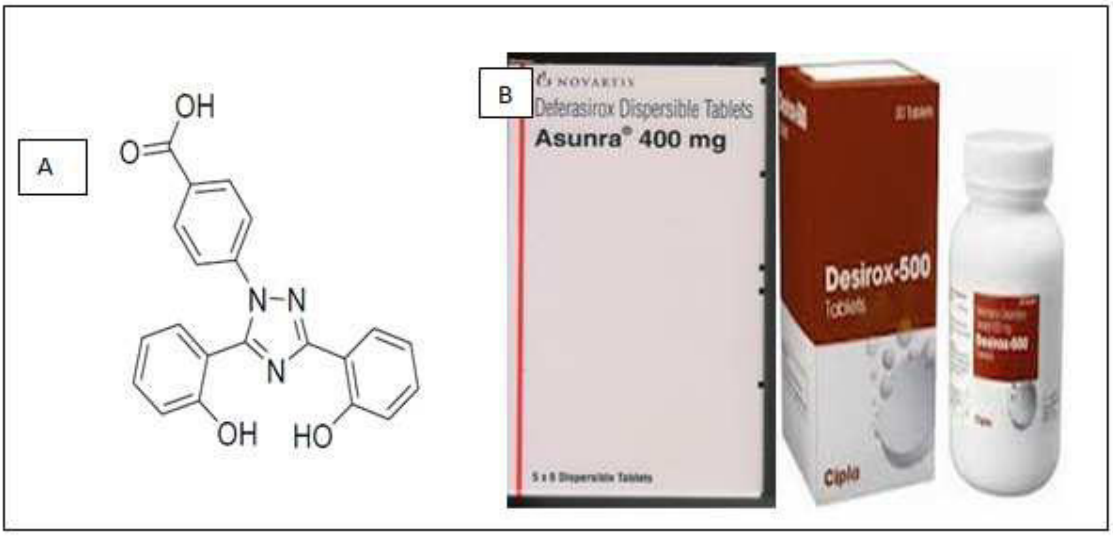

Figure 11
(A)DEFERASIROX [Tridentate (2:1) Low MW].
(B) Asunra, Desirox as marketed in India.

Dose

DFX shows dose-dependent effect on serum ferritin. Initially, in case of iron overload, this drug is started at 20 mg/kg/day orally once a day & then it may gradually increased @ 5-10mg/kg/day every 3-6 months. The maximum dose may be 40 mg/kg/day.

Side Effects

a. Transient gastrointestinal events including abdominal pain, nausea, vomiting, diarrhoea which lasted a median of 8 days or less.
b. Increase in Serum Creatinine in 1/3 rd of patients [47, 50, 51, 52, 53, 54] but generally never exceeded 2 times the upper limit.
c. Elevated liver enzymes (0.3 %) [50]

d. Neurosensory deafness or hypoacusis.
e. Urinary β-2 microglobulin was elevated in all patients but tended to normalize despite continuation of study [55].
f. In 2010, Novartis included a boxed warning about the risk of renal & hepatic failure as well as gastric haemorrhage.

Table-2
Comparison of Iron Chelators.

Property	Desferrioxamine(DFX)	Deferiprone(DFP)	Deferasirox(DFX)
Chelator: Iron Binding	1:1	3:1	2:1
Route of adminstration:	Subcutaneous/Intravenous	Oral	Oral
Half-life	20 mins	2-3 hrs	8-16 hrs
Route of excreation	Urine/stool	Urine	Stool
Usual dosage:	25-50mg/kg/day	75 mg/kg per day	20-30 mg/kg per day
Schedule:	Over 8-24 hours, 5-7 days per week	Three times a day	Daily once
Adverse effects:	Local reactions, Auditory, Ophthalmologic, Neurologic, Infectious, Pulmonary	Agranuloctyosis/neutropenia Arthralgia /Arthritis	Gastrointestinal disturbances, Hepatic and Renal Insufficiency
Advantages:	Long term safety of drug noted	Superior in Chelating Cardiac iron	Once daily dose. Effective iron chelator at high dose.
Disadantages:	Toxicity. Compliance problems.	Frequent blood count monitoring required	Long term data-not available.
Drug cost: (approx)	Rs 170/0.5gm Total cost- Rs.6000/month	Rs 350/50*500mg Cap. Total cost- Rs 1500/month.	Rs 3000/30*400mg Tabs. Total Cost- Rs 10,000/month

Adapted from Ref: 56..

COMBINATION THERAPY

For the last 12-15 years, more emphasis has been given on combination therapy, i.e. use of more than one iron chelators at a time. The combination iron chelation protocol states the use of two iron chelators alternatively, simultaneously or sequentially. The ideal, effective and gold standard chelation therapy till date is the use of Desferrioxamine along with Deferiprone. However, after the success of Deferasirox, Combination therapy is been more centralised on Desferrioxamine with Deferasirox, and also Deferiprone with Deferasirox. Combination therapy decreases the cost, toxicities, and dose and increases compliance and efficacy of iron chelation**.**

Various combinations of Iron Chelators and their Efficiency in Iron chelating.

Desferrioxamine + Deferiprone

Especially in the treatment of cardiac dysfunction due to secondary iron overload; Deferiprone shows potential advantage as it has the ability to mobilize iron from iron pools within parenchymal & reticulo-endothelial cells. Combination results in Synergistic effect of different binding characteristic of drugs [57]. Based on studies of Gomber et al,2004 and Galanello et al,2006; it has been suggested that serum ferritin can be controlled with a relatively low dose of DFO given twice a week, when administered along with DFP at standard dose. This therapy has proven outcomes in reversing myocardial siderosis, endocrinological complications. Simultaneous (Shuttling of iron leading to additional iron chelation) or sequential (24 hr exposure to iron chelation) administration are both being beneficial. DFO – 2 days + DFX – 7 days is the ideal protocol.

Desferrioxamine + Deferasirox

Have a shuttle effect, i.e. DFX works as an intracellular chelator & DFO as extracellular.

They are expected to produce synergistic effect leading to enhanced iron excretion from target specific iron compartments, less side-effects, improved compliance and

individualization of therapy. DFX accesses NTB pools unavailable to DFO alone. Hence, DFO & DFX produces additive effects and causes progressive both plasma NTB(Non Transferrin Bound) & LPI levels. It also shows higher potency without increase in side-effects.

Deferasirox + Deferiprone

Small scattered trials have been done with combination therapy with DFP and DFX. However promising results that have been evolved will claim for more use and more proven results and outcomes in near future. The mechanism of action of this combination is still not sorted out, but the result which few physicians has reported claims to be equivalent with DFO + DFP therapy.

ROUTINE MONITORING OF TOXICITY OF IRON CHELATORS

1. Audiometry.
2. Visual acquity, Refractometry, Retinoscopy.
3. Bone Mineral Density (Dexascan).
4. Serum Creatinine; Liver function tests.
5. Urine-Routine & Examination; Urine Total Protein, Albumin estimation
6. TLC, DC, Absolute Neutrophil Count.

Recent Advances

Few drugs are under research and in trial. SPD602 is in Phase 2 Clinical development. GT56-252 and FBS0701 are also thought to be ideal iron chelators. However, we eagerly wait for an ideal and safe iron chelator in near future.

IRON CHELATORS: A Ray of Hope for treatment of other diseases.

Iron chelating agents are now under trials and hope to show good results in treating neuro-degenerative diseases like Parkinsonism, Hallervorden-Spatz syndrome, Deferiprone has been used in Parkinsonism. Increasing body of evidence for the benefits of iron chelation in myelodysplasia, pre-stem transplant and treatment of Malignancies, will lead the use of iron chelators to be used into practice.

CONCLUSION

The fate of patients with chronic iron poisoning has completely changed with the introduction of the oral iron chelators. However, it is clear that, not a single iron chelator is fully efficient in decreasing iron overload from all the organs. Approach should me made to use combination therapy to get the best results. As the idea of the properties of an ideal iron chelator is clear, research efforts should be intensified in designing a safe and orally effective iron chelator.

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