Iron Deficiency: Advances in Diagnosis and Management

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ABSTRACT

Iron deficiency is the commonest haematological disorder encountered in practice. The basic approach to its diagnosis and management is well-established and outlined in standard textbooks of medicine and haematology. Our emphasis in this write-up is on recent advances in the field of diagnosis and management of iron deficiency (ID) and iron deficiency anaemia (IDA).

Diagnosis of IDA should be well-understood by every practicing clinician. Even though IDA is common in the developing world, it is not a very fascinating and challenging disease to investigate and treat. However, if properly investigated and treated, it is a fully curable disease with far reaching impact on quality of life. Although, not practical, evaluation of marrow for stainable iron is the most sensitive and reliable method for diagnosing iron deficiency and forms the gold standard. Tests like soluble transferrin receptor (sTfR) and erythrocyte zinc protoporphyrine (EZP) help in differentiating IDA from anaemia of chronic disease (ACD). Transferrin receptor: ferritin index is another innovative method to distinguish them from each other.

On the front of management, parenteral preparation should be resorted to in rare circumstances only. Conventional oral iron preparations are extremely useful. Iron polymaltose compounds are ineffective. If parentaral preparation is needed, iron gluconate in sucrose and iron sucrose are the safest.

INTRODUCTION

Iron is an important element in human metabolism. It is present in all cells of the body. Abnormalities in its metabolism have widespread effects. It has a central role in erythropoiesis. It is also involved in many other intracellular processes. Our increased insight into the physiological processes involving iron has helped in understanding and treatment of disease states. There is extensive literature describing iron compounds of biological importance. These range from myoglobin to enzymes concerned with mitochondrial electron transport, DNA synthesis, detoxification mechanisms, catecholamine metabolism and wide variety of other functions. It is therefore, not surprising that some of these compounds are affected by a state of ID. The haematologist's interest in iron metabolism has arisen from the common clinical manifestations of deficiency and some of the other less common pathological processes.

Homosapiens evolved and lived for several million years as a hunter-gatherer. He is adapted to absorb haem as an intact metalloporphyrin and to utilize the iron. The absorption of non-haem iron is limited in comparison, but is improved significantly when associated with aminoacids from animal proteins, ascorbic acid, sugars and acids from fruits. Anaemia is uncommon and iron nutrition is adequate in groups which have persisted as hunter-gatherers, including the Hadza in Tanzania and the ! Kung Bushman of the Kalahari Desert. The same is true of some pastoralists, including the Masai in Kenya, who supplement their food with blood and meat.

In evolutionary terms, the dawn of agriculture about 400 generations ago is a recent event to which Man has not adapted, and which has placed iron nutrition in jeopardy. Iron from grain staples is poorly absorbed, and as animal protein diminishes in the diet, the prevalence of nutritional iron deficiency rises. In addition, agriculture favours the transmission of the helminths which cause pathological loss of iron from the body. As a consequence of these two factors, iron deficiency has become one of the commonest disorder worldwide and in some populations, including Indian, it is almost universal resulting in a major health problem. In some areas, the absorption of iron may be further impaired by tropical sprue, a condition associated with agricultural water sources.

It remains debatable how much morbidity is associated with iron deficiency itself. It has been suggested that iron deficiency protects from heart disease and is also a defense against some infections. These are provocative ideas. Never the less, it is still generally agreed that iron deficiency, once recognized and certainly when symptomatic, requires treatment to raise the haemoglobin to an optimal level and to replenish iron stores.

Table 1: Laboratory diagnosis of iron deficiency

A. Screening
- Haemoglobin
- Mean corpuscular volume
- Percentage hypochromic erythrocytes
- Reticulocyte haemoglobin content
- Transferrin saturation
- Zinc protoporphyrin

B. Definitive
- Storage iron
- Serum ferritin
- Bone marrow haemosiderin
- Tissue iron
- Soluble transferrin receptor

The earliest stage of iron deficiency is termed iron depletion which is characterized by deficient iron stores without any decline in level of function compounds. The next stage is iron deficiency without anaemia which is characterized by decreased iron stores, low serum iron concentration and transferrin saturation but no anaemia. The third stage is frank iron deficiency anaemia (IDA) where besides reduced iron stores, low serum iron concentration and low transferrin saturation, there are low haemoglobin and haematocrit values.

Historically, the disease is characterized by pallor, dyspnoea and oedema and it was described in and around 1500 B.C. in Papyrus Ebers, a manual of medical therapeutics. Chlorosis was first described in 1554 by Johannes Lange. IDA most commonly affects women with poor diet, multiple pregnancies and menstrual irregularities.

LABORATORY DIAGNOSIS (Table 1)

Symptomatic IDA usually has Hb below 8 g/dl. The mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) are all reduced in IDA.[1] Anisocytosis, ovalocytosis, frank microcytosis and hypochromia, occurrence of target cells and elongated (so-called pencil) cells are commonly seen. Absolute eosinophilia is usually seen in hookworm infestation. Thrombocytosis is seen in 50-75% of patients. Platelet count may go up to twice the normal but return to normal level after therapy. The reticulocyte count is usually normal.

Red distribution width (RDW) is expressed either as co-efficient of variation (CV) or as standard deviation (SD) of which the RDW-CV is the most useful.[2] The normal value of RDW is 13.4 ± 1.2% (mean ± 2 SD); and in IDA it is 16.3 ± 1.8%. RDW in β or α - thalassaemia minor is 13.6 ± 1.6. RDW is highly sensitive (90-100%) but low in specificity (50-70%) in detecting iron deficiency anaemia. In β-thalassaemia minor, microcytosis is more severe and is not proportional to the severity of anaemia, but presence of basophilic stippling and more prominence of target cells should distinguish it from IDA. Quantitation of Hb-A2 is most helpful as it is elevated β-thalassaemia minor.

Distinction between IDA and anaemia of chronic disease (ACD) is usually not difficult. Anaemia, hypochromia and microcytosis are more marked in IDA; so is the degree of anisocytosis and poikilocytosis. However mild IDA may be difficult to segregate from ACD.

A dimorphic picture with microcytic hypochromic as well as normal population of red cells along with few heavily stippled hypochromic red cells are classically seen in sideroblastic anaemia (SA).

Bone marrow changes

Bone marrow exhibits both increase in cellularity and erythroid hyperplasia of mild to moderate degree. The erythroid cells are often smaller than normal (micro-normoblasts), have scanty cytoplasm with irregular ragged borders. It is important to assess the iron stores directly from the bone marrow. Haemosiderin is seen as golden yellow refractile granules in unstained bone marrow. But haemosiderin can be readily and reliable evaluated and graded after staining with Prussian Blue. Marrow haemosiderin stores are graded from 0+ and 6+. Normal marrow is graded 1+ to 3+ and in IDA, haemosiderin is absent.

Assessment of Iron Stores

The status of various iron pools can be evaluated by indirect, non-invasive methods, which are available in most laboratories. The so called iron profile constitutes serum iron level (SI), total iron binding capacity (TIBC), transferrin saturation (TS) and serum ferritin (SF).

Serum Iron

Serum iron is low. In most laboratories, the normal range for males is 75-175 µg/dl and in females, it is 10 µg/dl less.[3] It is influenced by large laboratory variables including iron medication prior to collection of blood sample.

Iron Binding Capacity (TIBC) and Transferrin Saturation (TS)

The average value of TIBC in both males and females is 340 µg/dl with a normal range of 250-450µg/dl.[4] Serum iron being in the range of 75-175µg/dl, the transferrin is found to be approximately one-third saturated. However, the normal reference range for transferrin saturation is 20-50%. The unsaturated iron binding capacity (UIBC) can be measured by spectrophotometric / colorimetric techniques or radioactive iron. TIBC is a mere summation of the UIBC and SI. In IDA, TS falls below 16% and both the UIBC and TIBC are raised.

In anaemia of chronic disease, the TS is often normal with a low SI levels.[5] The absolute value of TIBC is helpful in distinguishing IDA from ACD, since TIBC is decreased in ACD. However, if there is marked hypoproteinemia, the TIBC in IDA may also be decreased.[4]

Serum Ferritin

Serum ferritin estimation is the best non-invasive tests for evaluating body iron stores. Ferritin is primarily an intra-cellular iron storage protein, but small amounts of the same leaks into the blood stream. Adult males have a reference range of 20-500 µg/l and adult females 10-200 µg/l. Mean values in uncomplicated iron deficiency is around 3-6 µg/l and values greater than 12 µg/l are rare.[6] Different techniques are used to assess serum ferritin, of which the ELISA assay is the most employed; besides

the immuno-radiometric assay (IRMA) and radio-immuno assay (RIA). Serum ferritin loses its diagnostic value in the presence of infection, inflammation, ineffective erythropoiesis, malignancy and liver disease, in all of which it is elevated.[6]

Free Erythrocyte Protoporphyrin (FEP) / Free Erythrocyte Zinc Protoporphyrin (EZP)

Elevation of FEP, mainly the EZP level is an early and sensitive sign of iron deficiency, even in the latent phase of iron deficiency. FEP levels in normal red cells range from 15-80 μg/dl.[7] In uncomplicated iron deficiency anaemia, red cell FEP level range from 100-1000 μg/dl. Recent development of micro-extraction procedures and hemato-fluorometric methods has made this investigation easily available for diagnosis in contrast to the tedious time consuming macro-extraction methods. EZP is also elevated in ACD, chronic lead poisoning and sideroblastic anaemias. EZP in combination with serum ferritin levels have proved to be more specific and sensitive in detecting iron deficiency anaemia.

Soluble Transferrin Receptor (STfR)

Transferrin receptors (TfR) facilitate the entry of transferrin-bound iron into cells by a process of endocytosis. The STfR is a truncated form of the tissue transferrin receptor that consists of the N-terminal cytoplasmic domain, that has been proteolytically released from the cell membrane.[8]

Iron deficiency is the principal cause of elevated STfR. Unlike serum ferritin, it is not elevated in anaemia of infections and inflammations. Increased levels of STfR also occur with erythroid hyperplasia as seen in thalassaemia, sickle cell disease and other chronic haemolytic anaemias. On the other hand, decreased levels of circulating STfR are seen in patients with aplastic anaemia and chronic renal failure.[9]

STfR assay is based on quantitative immunologic techniques, i.e. ELISA assay. The normal reference value is 2.8-8.5 mg/l. STfR assays may be helpful in detecting co-existing iron deficiency in patients with known chronic inflammatory diseases like rheumatoid arthritis. The most sensitive method available to distinguish IDA from ACD is a combination of plasma STfR and the log of plasma ferritin concentration, i.e. STfR-ferritin index. If it is less than 1, it suggests ACD and if high i.e. >4, it indicates IDA.[10,11]

Reticulocyte Haemoglobin Cntent

It may be a new method for diagnosis of IDA and automated haemotology instruments may make it possible.

Iron Absorption

Various tests to evaluate iron absorption are useful as indirect measures of iron stores, since iron absorption varies reciprocally with the amount of stored iron. Direct measurement of iron absorption using radio-isotopes or total body counting techniques are too cumbersome as well as expensive.

MOLECULAR GENETICS OF IRON DEFICIENCY

Human transferrin gene is known to show many types of polymorphisms and it has been reported that human transferrin G277S mutation is a risk factor for iron deficiency. IDA was present in 27% women with homozygous G277S mutation, 10% with G277G/G277S heterozygous mutation and in 5% of women with homozygous wild type G277G/G277G.

DIFFERENTIAL DIAGNOSIS OF IDA

Different forms of anaemia that must be distinguished from IDA are thalassaemia minor, ACD, malignancy, sideroblastic anaemia, chronic liver disease, chronic renal disease, haemolytic anaemia and aplastic anaemia. Microcytic anaemias are the ones most confused with IDA and appropriate tests are required to distinguish between these disorders. When IDA is due to chronic blood loss, it is imperative to localise the site of blood loss and the nature of pathology by all available means. Atransferrinemia and antibodies to transferrin receptor are extremely rare disorders, but if detected, each case will find its place in academic hematology.

THERAPEUTIC TRIAL

Response to iron therapy is the proof of correctness of diagnosis of iron deficiency anaemia. Often the patient's response to therapy may become the primary diagnostic measure.

MANAGEMENT

Iron can be replaced either orally or by parentaral route. Replacement through oral route is generally the preferred method to treat iron deficiency. Once it has been established that patient is deficient of iron, replacement therapy should be instituted immediately. Iron can be administered most economically, in the highest required dosage and in the most assimilated form as simple iron salts.

General therapeutic principles of oral iron therapy[12-21]

Iron content of the diet is important, however, it must be emphasized that dietary iron alone is not sufficient to treat iron deficiency anemia. There are essentially two forms of iron present in diet: heme iron and non-heme iron. Heme iron is found in meat and poultry product. It has good bioavailability, although, the total amount of iron in meat is not high. The vegetarian diet has non-heme iron. It is absorbed poorly because of the inhibitory action of variety of dietary components like tannic acid and phytates.

For these reasons medicinal iron is essential in the therapy of IDA.

The dose of iron preparation is best calculated in terms of elemental iron. The average dose for adult with IDA is about 150 mg of elemental iron per day. It is given in 2-3 equal doses. Children weighing 15-30 kg may take half of the average adult dose. Small children and infants can tolerate relatively high dose i.e. 2-3 mg/kg/day and even up to 5 mg/kg/day. Mild degree of iron deficiency, where there is no haste to correct the hemoglobin deficit, can be managed with lower doses. However, it produces slower recovery.

Duration of oral iron therapy should be 4-6 months. Continued therapy replenishes the iron stores and decreases the chances of relapse.

Maximum iron absorption occurs in duodenum and upper part of jejunum. Therefore, iron from iron preparations should be readily released in stomach. Enteric-coated and prolonged-release

preparations dissolve slowly and are released beyond jejunum where absorption of iron is poor.

Iron is absorbed more completely when stomach is empty. When iron is taken with or immediately after the meals, absorption decreases by 40 to 50%. Acidic gastric pH is essential for iron absorption. Therefore, iron should not be given with medications that inhibit the production of hydrochloric acid in stomach. Antacid, H_2 receptor blocker and acid pump inhibitor like omeprazole can affect iron absorption.

Substances such as ascorbic acid (vitamin C),[12-14] succinate,[15] and fructose have been shown to increase iron absorption. Two hundred mg of ascorbic acid increases the absorption of iron by 30%. However, it also increases the frequency of side effects and there is no convincing evidence to support their concomitant use. Succinic acid also promotes iron absorption and unlike ascorbic acid, it does not increase the side effects. However, large amounts of succinic acid are required, approximately 180 mg for 35 mg of iron. Iron-succinic acid preparations are expensive (8 times more than ferrous soleplates).[15] Such preparations are not available in India.

Iron preparations

Ferrous salts

The iron should be quickly released and be readily absorbed. Since iron is absorbed in ferrous form; only ferrous salts should be used. Ferrous salts are absorbed about three times as well as ferric salts. Ferrous salts are the least expensive of iron preparations. Amongst the various ferrous salts i.e. sulphate, fumarate gluconate, there is a little variation in their bioavailability and tolerance. Ferrous sulphate is the hydrated salt, $FeSO_4, 7H_2O$. It has 20% elemental iron. Dried ferrous sulphate has 32% elemental iron. Ferrous flumarate contains 33% iron and is moderately soluble in water, stable and tasteless compound. Ferrous gluconate contains 12% of elemental iron.[12,13]

Iron-polysaccharide complex

Iron polysaccharide complex is a ferric-polysaccharide polymer.[16] It is alleged to be as effective as ferrous sulphate while causing fewer side effects. However, whether its absorption is as well as ferrous sulphate is in doubt. In addition, it is 8 to 10 times more expensive.[16]

Carbonyl iron

Carbonyl iron is actually metallic iron powder, with a particle size less than 5mm.[17] It is insoluble and is not absorbed until it is converted to the ionic form. The bioavailability of carbonyl iron is approximately 70% to that of equivalent amount of ferrous sulphate. Preliminary studies have indicated that carbonyl iron is potentially useful iron preparation. It seems to be absorbed as well as ferrous sulphate. It is considerably less toxic than ferrous iron. Resultant, it is not likely to lead to serious reactions in cases of accidental or suicidal ingestions. Carbonyl iron has lower frequency of adverse effects as well.[17]

It has slower release of iron. It is more expensive than ferrous sulfate. Tablets are available containing 45 mg and 60 mg of elemental iron, the adult dose being one tablet up to three times a day. In paediatric patients, it is prescribed as 3-6 mg/k/d divided into TID schedule. It is found to be safe in pregnancy.[17]

Response to oral iron therapy

Symptomatic improvement following oral iron therapy is fairly quick. Many patients show rapid subjective improvement in fatigue, lassitude and pica within 1 week.[18] The response occurs even before hemoglobin generation is observed. The earliest hematologic evidence of response to iron therapy is increase in the percentage of reticulocyte count. The reticulocyte count reaches its maximal value on 5th to 10th day of therapy. The maximal value is usually 5 to 10%. The rate of rise in hemoglobin varies depending on severity of anemia. It generally takes 2 months for hemoglobin to reach normal values. It generally reaches half way by day 18 of treatment.

Failure (non-responsiveness) to iron therapy

Unresponsive to iron therapy is not uncommon and is one of the frequent cause for referral to a hematologist. In such cases, following possibilities should be considered.

- Failure of the patient to take prescribed medicine: Even apparently intelligent and cooperative patients may fail to take medications as prescribed. To check on this possibility, the clinician might ask to bring back the empty packing or to bring the bottle for "pill counts".

- Inadequate prescription (dose, form, instructions). Iron preferably should be given on empty stomach in divided doses.

- Concurrent illness like rheumatoid arthritis, or associated folic acid or vitamin B_{12} deficiency causing dimorphic anemia

- Continuing iron loss: In some patients, blood loss is so great that oral iron therapy cannot keep up with it. Such patients do require parenteral therapy.

- Incorrect diagnosis.

- Absorption defect: rarely patient is unable to absorb the iron e.g. patients with partial gastrectomy or sprue.

Side effects of oral iron therapy

Most patients are able to tolerate oral iron therapy without much side effects, but 10-20% may develop symptoms attributable to oral iron. The most common side effects are gastrointestinal in the form of pyrosis (heartburn), constipation and diarrhoea. Some patients do develop heartburn, nausea and abdominal cramps. A metallic taste may be experienced. Most of the side effects are dose related. In a controlled study, iron was given in lower dosage 105mg/day. Incidence of side effects were similar in both placebo and a group which received iron.[19] The patient who is unable to tolerate the full therapeutic dose should be tried with smaller dose to start with and gradually full dose can be reached.

In many instances, both severity and frequency of side effects are exaggerated. In double blind controlled study, ferrous sulphate, ferrous fumerate, ferrous gluconate and placebo were administered in identically appearing tablets. All ferrous salts had similar incidence of side effects. No significant differences were noticed amongst the three iron salts.[20] Incidence of side effects was 13% in subjects taking placebo while 25% in those taking iron. Thus approximately 12% had symptoms ascribed to iron.[20] Side effects of oral iron therapy are not as common as

generally believed. With patience, persistence and with minor dose adjustment, oral iron regimen can be devised for virtually all patients.

Overdose of iron

Overdose of iron leading to iron-poisoning usually results after accidental ingestion of iron preparations intended for adult use by infants and small children. The earliest manifestations are vomiting, often associated with hematemesis. This is followed by hypotension, tachypnoea, restlessness and cyanosis. If amount ingested is large, within few hours patient goes into coma followed by death. Usually, if medical aid is sought early and proper treatment is offered, most children survive.[20]

The initial treatment is prompt evacuation of the stomach either by inducing emesis or gastric lavage. Gastric lavage should be done with sodium bicarbonate solution and at the end of lavage, 5 to 10 gm of Desferrioxamine solution with approximately 60 ml of sodium bicarbonate should be left in the stomach. Increased serum iron level does require intramuscular administration of desferrioxamine in doses of 0.5 to 1 gm. The children, who survive initial 3-4 days usually recover without much sequelae. Gastric stricture, fibrosis and intestinal stenosis are rare late effects.[20]

Parentaral iron therapy

Parentaral iron therapy is not more effective than oral. In addition, it is expensive and can be dangerous. It should never be prescribed routinely without one or more definite indications as enlisted below:[21]

- Poor compliance to oral therapy in spite of repeated counseling
- Intolerance to oral iron
- Rapid blood loss which is difficult for oral iron to compensate
- Gastrointestinal disorders where oral iron may exacerbate the symptoms i.e. peptic ulcer, ulcerative colitis
- Malabsorption syndromes
- Inability to maintain iron balance as seen in patients on haemodialysis
- Pregnant women with severe IDA, presenting late in pregnancy
- Patient donating large amount of blood for auto-transfusion programme

Calculation of dose

The total dose of iron to be administered can be calculated using following formula:

$$\text{Iron to be injected (mg)} = (15 - \text{patient's Hb as g/dl}) \times \text{body weight in kg} \times 3$$

Many other formulae are also available. However, the one described above is a simple one to remember. It includes the iron required to replenish the stores as well.

Route of administration

Parentaral iron can be given either intramuscularly or intravenously. It is mandatory to give a test dose prior to parentaral iron as the risk of anaphylaxis is high.

Intramuscular iron can be given daily or on alternate days. It may also be given once a week. Individual dose should not exceed 1.5 - 2.0 ml. The injections are continued until the total dose is administered. Injections are usually given deep intramuscularly in the upper and outer quadrant of the buttock using Z-technique. In this, the puncture site in the skin is away from the puncture site of the subcutaneous tissue. This prevents staining of the skin. The site for successive injections should be changed.[22]

Intravenous iron can be administered either by repeated undiluted injections or as a single total dose infusion.[23]

As undiluted repeated bolus injections, the total dose is calculated and 5 ml each is given at a sitting. It is preceded by a test dose, for which 0.5 ml of iron preparation is diluted with 5 ml of patient's own blood and it is administered intravenously slowly. Patient is observed for 30 minutes. If there are no reactions, the drug is given slowly at the rate of 1 ml per minute. The patient must be kept under observation for one hour after each injection has been completed. The needle used for aspirating the ampoule contents must not be used for I.V. injection as it could irritate the tissues. At any suspicion of extravasation, the administration must cease.

As total dose infusion (TDI), the calculated dose is diluted in 1 liter of saline.[24] The maximum concentration of iron must not exceed 2.5 g per 1 liter of saline. TDI must also be preceded by a test dose wherein 25 mg of the drug is diluted in 50 ml of normal saline and infused over 5 minutes. Patient is observed for an hour for hypotension, wheezing, dyspnoea, tachycardia and cutaneous rashes. If there is no reaction, the TDI is started and it is give over 4 hours. Throughout this period, close supervision is necessary. Emergency resuscitation measures are kept handy. Treatment of anaphylaxis must be instituted immediately, if required.[24]

Adverse reactions

The frequency of adverse reactions to parentaral iron is high (30%). These include the following:

- Anaphylaxis:[25] This is the most serious adverse effect. It is dose-independent. It occurs within first few minutes of drug administration including the test dose. It can occur anytime during the course of treatment. There have been incidences when the first few injections had no adverse effects, however, the subsequent one lead to anaphylaxis. Therefore, the resuscitation measures must be available during each injection. If anaphylaxis occurs, further parentaral iron therapy, including in future, is totally contraindicated.
- Arthralgia-myalgia syndrome: This is a dose-related phenomenon. It is not life-threatening. It may occur in nearly 1/3rd of patients. It may be delayed and occur at a later stage. There may be associated fever and skin rash.
- Urticaria
- Generalised lymphadenopathy
- Acute febrile illness: This may be accompanied by maningismus, lymphadenopathy, splenomegaly and investigations may show leukocytosis (neutrophilic), raised ESR and CSF pleocytosis
- Skin discoloration: Gray or black discoloration of the skin at the site of injection. This may persist for ever.

Table 2: Comparison of iron dextran and ferric gluconate

	Iron dextran	Ferric gluconate
Maximum dose (mg of iron)	500 - 1000	125
Test dose required	Yes	No
Administration time	2-4 hours	15 minutes
Utilization time	Weeks	Days
Reactions		
Anaphylactic	Uncommon (0.61%)	Very rare (0.04%)
Delayed	Common (2.5%)	Uncommon (0.4%)

- Tenderness: Severe pain and tenderness at the site of injections are common events.

Preparations

There are various parentaral iron preparations. Some are not yet available in India.

Iron dextran (Imferon, Ferri^{tm})

Iron dextran (Imferon, Ferri™)

Iron dextran is the earliest of parentaral iron preparation. It is a colloid of ferric hydroxide with dextran. Each ml contents 50 mg of elemental iron. It may be administered intramuscularly or intravenously. It is the most widely used parentaral preparation. It is available in a dark brown, colloidal suspension. As mentioned earlier, the dose is calculated from the deficit in body iron, with allowance both for iron to correct the haemoglobin deficit and for iron to rebuild stores. Life-threatening, immediate anaphylactic reactions is the most serious risk and it occurs in 0.5 - 1.0% of patients. It may have a fatal outcome, despite treatment. Delayed but severe serum sickness-like reaction may develop in a substantial proportion of patients. It is characterized by fever, urticaria, adenopathy, myalgias and arthralgias. It can exacerbate arthritis in patients with ankylosing spondylitis as well as rheumatoid arthritis.

With IM injections, local reactions including skin staining, muscle necrosis, phlebitis and persistent pain at the site of injection could occur. In animals given massive doses of iron dextran, sarcomas have developed; however, no similar evidence of a carcinogenic risk in humans has been presented.

Although test dose is recommended, the value of this precaution is limited because anaphylaxis can occur with the test dose itself. Hence, iron dextran should be administered parentarally only if the facilities and medical expertise for managing the anaphylactic reactions are available. Another way of giving iron dextran which may be more convenient and less hazardous is to administer the total dose of iron dextran in a single intravenous infusion. The manufacturer suggests a total dose of 40 ml of iron dextran (the equivalent of 2000 mg or iron) for an iron-deficient 70 kg individual with a haemoglobin level of 7 g/dl.

Despite these risks and restrictions, parentaral iron therapy is still preferred for those patients who cannot be managed with oral iron as the hazards and expenses of blood transfusion are even greater.

Iron sorbitol citrate (Jectofer)

This is a complex of iron, sorbitol and citric acid. This compound is only for intramuscular use. Each ml contents 50 mgm of elemental iron. It is rapidly absorbed from the site of injection. Thirty percent of the drug is excreted in the urine within 24 hours. This must be adjusted while calculating the total dose. It is usually given as 10-20 deep I.M. injections over 2-3 weeks. The injections are painful and they also lead to skin staining as well as arthralgia.

Ferric gluconate (Globac, Efficient)

Sodium ferric gluconate complex in sucrose[26] is a newer form of parentaral preparation available for therapeutic use. It is safer than iron dextran and iron sorbitol citrate. It is available in two strengths: 62.5 mg/ml and 125 mg/ml. It is given intravenously as a series of injections usually as infusions. It cannot be given as a single large dose as it rapidly releases iron from the complex leading to over saturation of transferrin. Once this occurs, circulating free iron leads to oxidative stress and hypotension. This preparation is very well tolerated and incidence of adverse reactions is low. However, occasional patient can get hypotension, nausea, vomiting, myalgia and hypersensitivity reactions characterized by bronchospasm, laryngeal oedema or even cardio-vascular collapse (extremely rare). It is popularly used by nephrologist with rHuEPO therapy, during dialysis.[26]

Table 2 compares iron dextran vs ferric gluconate.

Iron sucrose (Venofer)

This form of parentaral iron is different from iron gluconate in sucrose. It is a complex of polynuclear iron (III) - hydroxide in sucrose.[26] It is available as 5 ml single dose vial. It contains 20 mg/ml of elemental iron. It is only for intravenous use. It is relatively free from adverse effects and some trials have advocated dropping of a test dose. However, it is safer to give a test dose. Each vial of 5 ml can be given slowly over 5 minutes intravenously. It may also be given in the form of an infusion containing 5 ml per 100 ml of normal saline infused over 15 minutes.[26] Rapid administration in a patient with low iron binding capacity can lead to free circulating iron causing adverse reactions. This form of iron cannot be given as a single total dose infusion. Rarely, life-threatening reactions have also been reported. Osteomalacia, secondary to hypophosphatemia has also been reported. This may be due to its effect on kidney or bone. Other rare adverse effects include nausea, vomiting, diarrhoea, headache, muscle cramps and hypotension.

This preparation has been approved for use in US in late 2000, although, it has been used in Europe for several decades.

Assessment of response

The response assessments can be done by reticulocyte count. Increase in reticulocyte count may be noted by 5th day and it peaks by 10th day. The rate of rise of Hb is inversely proportional to initial Hb level. Usually, Hb rises by 2 g/dl in 3 weeks. Serum iron gradually increases and total iron binding capacity returns to normal in a month's time.

CONCLUSION

In conclusion, parentaral iron therapy should be used sparingly. Oral iron replacement remains the treatment of choice. The indications for parentaral iron therapy must be critically analyzed. If it has to be administered, it must only be done by experienced practitioners with adequate facilities to prevent life-threatening

events. At the same time, parentaral iron therapy, especially total dose infusion remains an extremely useful therapeutic tool in a given situation.

REFERENCES

1. Bainton DF, Finch CA. The diagnosis of iron deficiency anaemia. *Am J Med* 1964;37:62-65.
2. Viswanath D, Hegde R, Murthy V, Nagashree S, Shah R. Red cell distribution width in the diagnosis of iron deficiency anaemia. *Ind J Pediatr* 2001;68;1117-9.
3. International Committee for Standardization in Haematology. Recommendations for the measurement of serum iron in human blood. *Br J Haematol* 1978;38:291-97.
4. International Committee for Standardization in Haematology. The measurement of total and unsaturated iron-binding capacity in serum. *Br J Haematol* 1978;38:281-90.
5. Bainton DE, Finch CA. The diagnosis of iron deficiency anaemia. *Am J Med* 1964;37:62-69.
6. Finch CA. Plasma ferritin determination as a disgnostic tool. *West J Med* 1986;145: 657-66.
7. Zanella A. Sensitivity and predictive value of serum ferritin and free erythrocyte proto-porphyrin for iron deficiency. *J Lab Clin Med* 1989; 113:73-80.
8. Skikne BS, Flowers CH, Cook JD. Serum transferrin receptor: A quantitative measure of tissue iron deficiency. *Blood* 1990;75:1870-1876.
9. Gaillard T, Fontan E, Civadier C, Emile L. Laboratory study of a new marker of iron deficiency diagnosis : the soluble transferrin receptor. *Ann Biol Cin* 2001;59:632-635.
10. Rimon E, Levy S, Sapir A, et al. Diagnosis of iron deficiency anaemia in the elderly by transferrin receptor – ferritin index. *Arch Intern Med* 2002; 162:445-49.
11. Punnonen K, Irjala K, Rajamaki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. *Blood* 1997;89: 1052-7.
12. Grebe C. Effect of meals and ascorbic acid on the absorption of therapeutic dose of iron as ferrous and ferric salts. *Curr Ther Res* 1975;17:382-86.
13. Brise H. Hallberg L. Iron absorption studies. *Acta Med Scand* 1962;171 (Suppl 376):1-11.
14. Hallberg L. Studies on oral iron therapy. *Acta Med Scand* (Suppl) 1966; 459:3-10.
15. Hallberg L, Norrby A, Solvell L. Oral iron with succinic acid in the treatment of iron deficiency anemia. *Scand J Haematol* 1971;8:104.
16. Tinawi M, Martin KJ, Bastani B. Oral iron absorption test in patients on CAPD: comparision of ferrous sulfate and a polysaccharide ferric complex. *Nephron* 1996;74:291-294.
17. Gordeuk VR, Brittenham GM, Hughes M, Keating LJ. High dose carbonyl iron for iron deficiency anemia: A randomized double-blind trial. *Am J Clin Nutr* 1987;46:1029-38.
18. Coltman CA Jr. Pagophagia and iron lack. *JAMA* 1969;207:513-24.
19. Cook JD. Iron deficiency anemia. *Baillieres Clin Haematol* 1994;7: 787-98.
20. Kerr DNS, Davidson S. Gastrointestinal intolerance to oral iron preparations. *Lancet* 1958;2:489-95.
21. McCurdy PR. Oral and parenteral iron therapy: a comparison. *JAMA* 1965;191:859-63.
22. Amitai A, Acker M. Adverse effects of intramuscular iron injection. *Acta Haematol* 1982;68:34148.
23. Hamstra RD, Block MH, Schock, et al. Intravenous iron dextran in clinical medicine. *JAMA* 1980;243:1726-32.
24. Lane RS. Intravenous infusion of iron dextran complex for iron deficiency anemia. *Lancet* 1964,1:852-56.
25. Becker CE, McGregor RR, Walker KS, et al. Fatal anaphylaxis after intramuscular iron dextran. *Ann Intern Med* 1966;65:745-51.
26. Faich G, Strobos F. Sodium ferric gluconate complex in sucrose: safer iv iron therapy than iron dextran. *Am J Kidney Dis* 1999;33:464-470.