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REVIEW

Understanding the management of iron deficiency anaemia

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Abstract

Iron deficiency, the most common cause of anaemia, is seemingly easy to manage. However, in many cases the nutritional deficiency is complicated by concurrent gastro-intestinal disease and/or inefficient absorption. In addition, iron absorption and mobilisation from physiological storage sites is regulated by the peptide hormone hepcidin, which is upregulated in anaemia associated with chronic inflammation. Successful patient management requires the continuous evaluation of iron status as well as monitoring of haemoglobin levels to measure treatment outcomes. Iron requirements change with patient physiological status and this must be taken into consideration when making clinical decisions. Provided that there is no underlying problem most patients respond rapidly to oral iron therapy. In non-responsive patients, and patients with concurrent gastro-intestinal disease, parenteral therapy must be considered. This brief review provides a summary of some of the problems that may be encountered with the management of iron deficiency and iron deficiency anaemia.

Introduction

In the management of anaemic patients, the type and severity of the anaemia will dictate the appropriate therapeutic strategy. Globally, iron deficiency is the most common cause of anaemia.[1] Once iron therapy is initiated, regular follow-up visits are essential to monitor the therapeutic response, and to manage unpleasant adverse effects which may compromise patient compliance. Irrespective of the presence or absence of anaemia, iron deficiency decreases the quality of life and increases the risk of serious health issues.[2]

Apart from its well-known function as an oxygen carrier in haemoglobin and myoglobin, iron is required for the efficient functioning of numerous other haem and non-haem enzymes. Cytochromes, essential for the process of oxidative phosphorylation and generation of ATP in all cells, require iron to function effectively.[3] Therefore, iron deficiency has a negative impact on cellular respiration and ATP production, which in turn, decreases DNA synthesis and cell division.[4]

Who requires iron supplementation?

Patients with an inadequate intake of nutritional iron are at risk of developing iron deficiency anaemia, which is characterized by microcytic hypochromic red blood cells. Patients who present with iron deficiency but without anaemia show a collection of non-specific symptoms which include generalised fatigue, weakness, inability to concentrate, and decreased cognitive performance.[3,5] It is important to determine total body stores of iron in both anaemic and iron deficient patients.

The physiological demand for nutritional iron is increased in specific population groups:[6]

- Premature infants, children and adolescents undergoing growth spurts
- Pregnant and lactating women
- Patients with chronic kidney disease (erythrocyte loss during haemodialysis)
- Patients receiving erythropoietin
- Patients that suffer from chronic blood loss - menstruating women, bleeding from the gastro-intestinal tract (GIT).

Diet affects iron status

Unlike haem iron, a vegetarian diet decreases total iron stores as iron from plant sources is poorly absorbed from the GIT. Meals rich in dairy products decrease the absorption of iron. High fibre meals and cereals bind iron and reduce its absorption from the GIT.[6]

Hepcidin and iron homeostasis

There is no excretory mechanism for iron, which is conserved in the body by recycling when senescent red blood cells are engulfed by macrophages. Under normal physiological conditions, GIT absorption of iron is restricted (1–2 mg daily) to prevent its accumulation to toxic levels. In iron deficiency anaemia, absorption of iron from the GIT is increased.[8] Both iron recycling from senescent erythrocytes and its absorption

Table I: Recommended daily allowance (mg/day) and daily requirement (mg/kg/day) of elemental iron

		RDA mg/day	Daily requirement mg/kg
Infants	0–8 months	*	-
	Low birthweight (2–2.5 kg)	Supplementation 1–2 mg/kg/day	
	7–12 months	11	67
Children	1–3 years	7	22
	4–8 years	10	22
	9–13 years	8	22
Adolescents	Males: 14–18 years	11	21
	Females: 14–18	15	20
Men	Older than 19 years†	8	13
	Vegetarian men	14	
Women	19–50	18	21
	Over 50†	8	13
	Vegetarian pre-menopausal	33	21
	Pregnancy	27	80
	Breastfeeding (< 18)	10	
	Breastfeeding (> 18)	9	

*No RDA is available for healthy infants. Adequate intake is considered to be 0.27 mg/day. Formula should be fortified.
† Unless there is a clinical indication, iron supplementation is not indicated in adult men and post-menopausal women, since iron supplements in these patients may lead to iron-overload.[7]

from the GIT are controlled by the hormone hepcidin.[9] Hepcidin responds to increased plasma and tissue iron levels by stimulating the degradation of ferroportin, the protein responsible for the export of iron from cells.[10] In iron deficiency, the synthesis of hepcidin is suppressed and the absorption of iron from the GIT increases.[11]

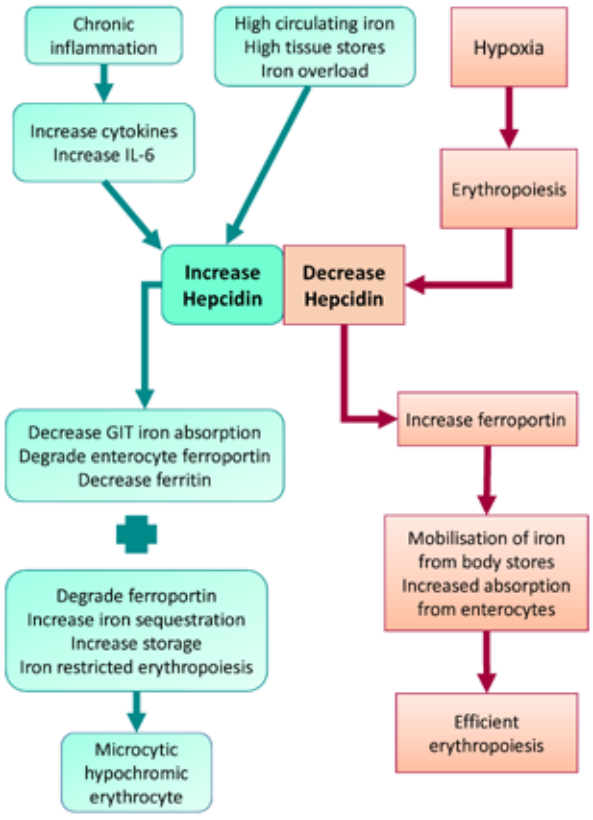

Figure 1: Hepcidin regulates iron absorption and mobilisation from internal stores, and is increased in chronic inflammatory disease states.

Aetiology of inefficient GIT absorption of iron

Several factors decrease the absorption of iron from the GIT and complicate the management of iron deficiency anaemia:

- Parasitic hookworm and schistosomiasis infestations contribute to chronic blood loss and iron deficiency.[12]
- *Helicobacter pylori* competes with its human host for orally ingested iron, decreases vitamin C levels and causes bleeding from micro-erosions.[13]
- Iron deficiency is an atypical manifestation of coeliac disease.[14,15]
- Patients with chronic inflammatory bowel disease frequently have concurrent folic acid and vitamin B_{12} deficiency, and their anaemia is associated with chronic inflammation.[16] Since oral iron supplementation aggravates gastric inflammation, parenteral iron is preferred in these patients.
- Chronic inflammatory states upregulate the synthesis of hepcidin which decreases the gastrointestinal absorption of iron.[15,17] Use of nonsteroidal anti-inflammatory drugs (NSAIDS) to counteract inflammation cause GIT bleeding.
- Proton pump inhibitors interfere with iron absorption, and their widespread use frequently contributes to unexplained iron deficiency anaemia.[18]
- Bariatric surgery removes iron absorption sites from the GIT, and increases gastric pH.[19]
- Iron refractory iron-deficiency anaemia is defined as a failure to respond to oral iron therapy after 4 to 6 weeks (an increase of less than 1 g haemoglobin) in the absence of any other contributing factors. It is caused by a rare autosomal recessive disorder that increases the production of hepcidin, preventing iron absorption.[20]

Therapeutic strategy

Available iron preparations

Oral and parenteral iron preparations are available for therapeutic use. Parenteral iron must be considered when there is no therapeutic response after three to four weeks of oral supplementation. Failure to respond to iron therapy suggests continuing blood loss, incorrect diagnosis, non-adherence, and malabsorption. Severe and persistent gastrointestinal intolerance is another indication for parenteral iron.

Oral iron therapy

Oral preparations include the ferrous salts; ferrous fumarate, ferrous sulphate and ferrous gluconate salts as well as ferric polymaltose complexes. These preparations are equivalent in terms of therapeutic efficacy and contain various amounts of elemental iron which should be taken into consideration when calculating dosages.[7]

Iron is also formulated in combination with folic acid, vitamin C and vitamin B_{12}. This increases the cost of the preparations without benefit to patients. Iron combined in multivitamin and/or mineral supplements is best avoided since there is a high potential for polycomponent interactions that decrease absorption. Iron absorption is impaired by calcium, carbonates and phosphates, common ingredients of multivitamin and mineral supplements.[6,7]

In patients with severe iron deficiency and depleted stores, iron therapy must be continued for a period of three months after haemoglobin levels are corrected, to replenish iron stores.[6,7] The therapeutic dose of oral iron for adults is between 100 and 200 mg/day of an iron salt preparation, given in divided doses. In infants, the dose of elemental iron is 1–2 mg/kg/day for iron deficiency, and 1mg/kg/day for prophylaxis. Preterm infants should receive a dose of 2 mg/kg/day after their birthweight has doubled. A dose of 3–6 mg/kg/day is recommended for older children. Further information on recommended daily dosages can be found in the South African Medicines Formulary (SAMF), 12th edition.

Iron absorption, transport, storage and elimination

Absorption

Approximately 25% of orally administered iron is absorbed from the GIT of anaemic patients and takes place from the duodenum and the proximal jejunum. Iron in the reduced, ferrous (Fe^{2+}) state, is absorbed more efficiently than iron in the ferric (Fe^{3+}) state.[21]

Iron crosses the luminal membrane of the intestinal mucosal cell by two mechanisms:

i. Active transport of ferrous iron by the divalent metal transporter 1 (DMPT1).

ii. Absorption of iron complexed with haem, which is later split from the haem molecule.

Iron is then transported across the basolateral membrane by ferroportin and oxidized to the ferric (Fe^{3+}) state.

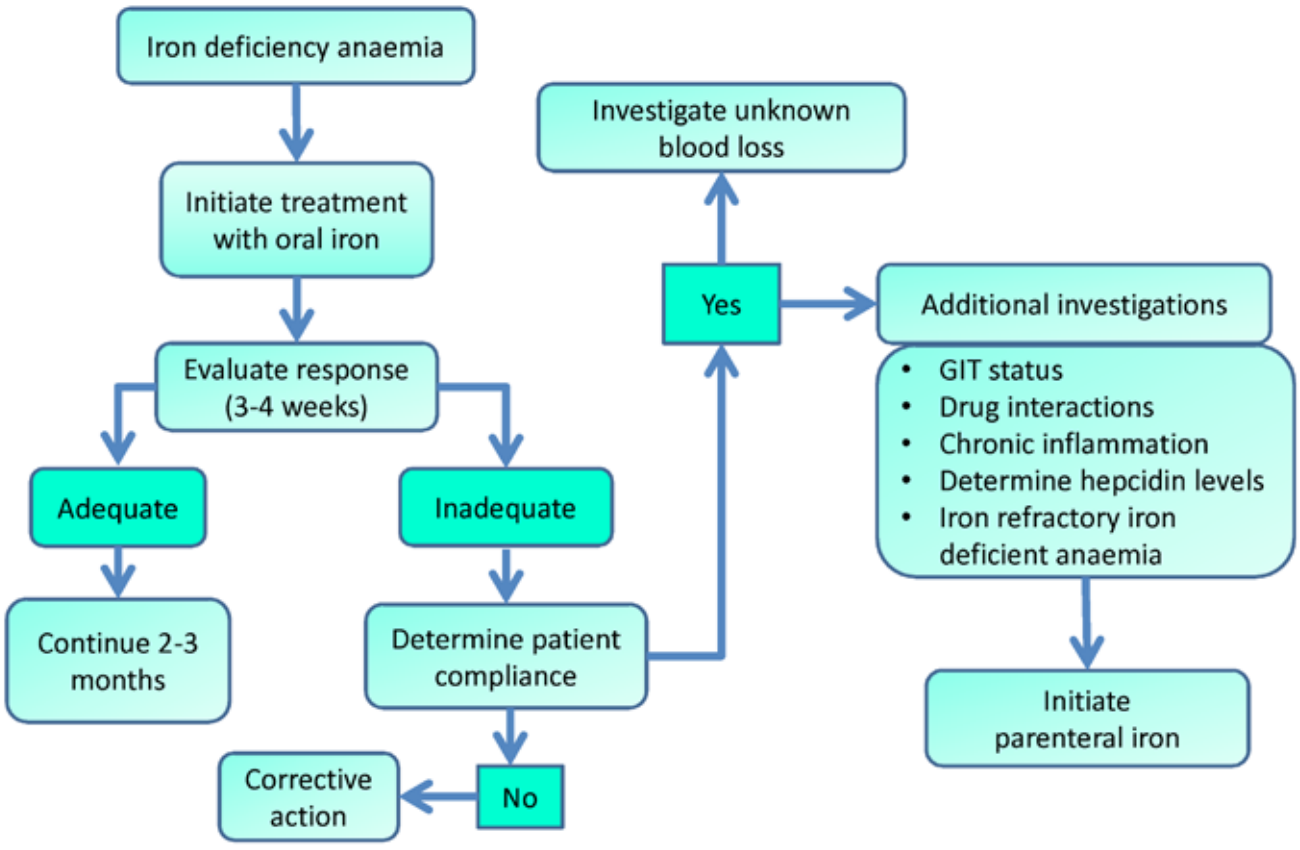

Figure 2: Flow-diagram outlining the management of the iron deficient anaemic patient

Transport

In plasma, iron is transported bound to transferrin. This complex enters maturing erythroid cells by binding to transferrin receptors followed by receptor mediated endocytosis. The iron is released, reduced to ferrous iron and then either used in haemoglobin synthesis or stored as ferritin.[22]

Storage

Iron is stored as ferritin in intestinal mucosal cells, spleen and bone, and in parenchymal liver cells. Its mobilisation is controlled by hepcidin.

Elimination

There is no mechanism for the elimination of iron. Small amounts are lost in faeces by exfoliation of intestinal mucosal cells.[23]

Adverse effects of oral iron therapy

These are mainly dose related GIT adverse effects which manifest as heartburn, nausea, abdominal cramps, constipation, and diarrhoea. The effects can be reduced by decreasing the dose, or by taking the iron preparations with meals. Food decreases the absorption efficacy of orally administered iron by 30–50%. In addition, oral iron therapy causes black stools that obscure the diagnosis of occult blood loss. Unless occult blood loss is present, the dark stools have no clinical significance.[6,7]

Parenteral iron therapy

Parenteral iron therapy is reserved for patients unable to tolerate or absorb oral iron or patients with severe chronic anaemia, caused by advanced chronic renal disease, gastrectomy or small bowel resection.[24] Hypoxia associated with severe iron deficiency can cause cardiovascular symptoms like heart failure and angina. These patients require a blood transfusion to rapidly correct the hypoxia and improve their iron stores. A unit of packed red blood cells provides approximately 200 mg of iron.[5] Parenteral iron rapidly increases haemoglobin levels and corrects total iron stores. Both intravenous and intramuscular preparations are available. When parenteral therapy is started, oral iron administration must be stopped to prevent iron overload.

Parenteral iron preparations carry the risk of anaphylactic reactions and also have a high potential for adverse reactions.[25,26] The administration of a small test dose is advised, since anaphylactic reactions are unpredictable. Iron dextran solutions are more likely than other preparations to cause anaphylactic and hypersensitivity reactions.[27] Procedures to manage anaphylaxis and hypersensitivity reactions must be in place before administration of parenteral iron. Patients requiring chronic parenteral iron therapy must have total body iron stores monitored, to prevent iron overload.

Parenteral iron preparations available in SA:

i. iron polymaltose (IM only)

ii. ferric hydroxide sucrose complex (IV only)

iii. iron hydroxide-dextran (IM or IV)

Adverse reactions of parenteral iron therapy

Intramuscular iron injections are painful and cause staining of the skin. Other adverse effects common with parenteral iron therapy include; headache, fever, arthralgia, nausea and vomiting, back pain, flushing, urticaria and bronchospasm.[25,26,27]

Iron supplementation during erythropoietin therapy

Iron status must be determined prior and during erythropoietin therapy, since the massive haematopoietic drive will put pressure on available iron stores. Similar effects on iron stores are seen in the treatment of severe megaloblastic and pernicious anaemias. It is therefore important to ensure an adequate supply of iron when treating patients with these conditions.[28,29]

Acute iron poisoning

Most cases of acute iron poisoning occur in children and are potentially fatal. Iron causes the formation of hydroxyl radicals that cause necrotizing gastroenteritis. Patients develop haematemesis, GIT perforation, vascular collapse, metabolic acidosis, cyanosis, hypoglycaemia, pulmonary oedema, hepatorenal failure and ultimately convulsions and coma. Despite an apparent improvement after initial presentation, acidosis develops and patients may die. Acute iron poisoning must be treated urgently by gastric lavage or whole bowel irrigation, and deferoxamine which chelates iron. Patients require intensive supportive therapy to maintain acid base status.[6,7]

Summary

- Determine the cause and severity of the iron deficiency / iron deficiency anaemia.
- Initiate therapy with oral supplementation.
- Monitor patient response and manage adverse effects.
- Patients not responding to oral iron therapy require further investigations.
- Initiate parenteral therapy if patient is not responding to oral therapy.
- Continue supplementation until iron stores are replenished.

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