Oral Liposomal Iron: A Treatment Proposal for Anemia

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Shortcomings of oral iron supplementation are: (1) Poor iron absorption (10–15%), (2) iron loss or iron requirements in excess of the absorbed dose, (3) low bioavailability, (4) poor tolerability, (5) leading to noncompliance. Iron absorption can be lowered by concomitant intake of iron absorption inhibitors like phosphates, phytates, and tannates in food and certain digestive disorders. Certain side effects like abdominal discomfort, nausea/vomiting, diarrhea, and/or constipation are directly related to the amount of elemental iron ingested.1,6,8,9

Intravenous (IV) iron is recommended as second-line therapy for patients who do not respond to oral iron, who have intolerance to oral iron, or who are noncompliant with oral iron therapy, require rapid iron replacement, malabsorption due to surgery, heavy bleeding, concomitant use of erythropoietin, and anemia secondary to cancer or chemotherapy.1,10 Some of the IV preparations available are iron gluconate, iron hydroxide sucrose complex, and iron dextran.7 In spite of their good safety profiles, IV iron preparations are painful, require patient monitoring and carry the risk of anaphylaxis and certain preparations can cause injection site discoloration.7,10

LIPOSOMAL DRUG DELIVERY

English hematologist Alec Bangham in 1961 first described the liposomes and since then they have been recognized and extensively used as delivery vehicles for pharmaceuticals.11

Liposomes are spherical vesicles characterized by a bilayer of lipids with an internal aqueous cavity. Liposome structural components are phospholipids or synthetic amphiphiles incorporated with sterols. This phospholipid bilayer is suitable for fundamental cellular functions, such as motility and shape change, and provides also the ability to mimic the biophysical properties of living cells (Fig. 1). Two delivery areas where liposomes have shown most promise are drug delivery and gene therapy, owing to the advantages that their use brings over traditional methods. In the area of drug, most liposomal drug formulations are approved for IV application; intramuscular and oral delivery have also been examined. Liposomes are biphasic and therefore render them the ability to act as carriers for both lipophilic and hydrophilic drugs. Encapsulation of drugs in liposomes enhanced the therapeutic indices of various agents, mainly through alterations in their pharmacokinetics and pharmacodynamics.12,13
The characteristics of the liposomes can be altered according to the different substances carried. For example, it can decrease the speed of degradation of the liposome and slow down the release of its content. The affinity of liposomes for a given tissue can be increased by varying its composition and electrical charge or even adding adhesive receptors or antigens.

**ORAL LIPOSOMAL IRON**

Iron salts like ferrous pyrophosphate are covered with liposome, a spherical structure of a phospholipidic nature that is similar to those human cell membranes. This preparation crosses the gastric acid barrier and reaches the small intestine intact. In the intestine, the M cells due to their low lysozyme content integrally absorb liposomal iron without the need for specific transporters (Fig. 2). Subsequently, the liposome is incorporated by endocytosis from macrophages and through the lymphatic stream it reaches, intact, the hepatocytes. The liposomal protection allows the iron to overcome the free gastric environment, preventing early degradation of the substance and/or its inactivation and to be absorbed directly. This mechanism provides liposomal iron a greater availability, reduces gastrointestinal side effects, and prevents iron instability in the gastrointestinal tract to be directly absorbed into the intestine and directly liberated into the liver.

Consequently, this method of iron supplementation is associated with high gastrointestinal absorption, high bioavailability, and a low incidence of side effects. The absorption or bioavailability of liposomal pyrophosphate iron is 3.5 times greater than the free pyrophosphate iron, 2.7 times higher than iron sulfate, and 4.1 times higher...
compared with iron gluconate. In addition, the plasma concentration of liposomal iron was maximum after 2 hours from the assumption, which guarantees greater bioavailability of the element for all metabolic processes.\(^{14}\) However, the transportation of iron can be regulated by the size of liposomes, and it decreased with particle size increasing. Furthermore, depending on the size of liposome, different pathways, such as altering signaling processes essential for basic cell functions, receptor-mediated endocytosis, phagocytosis, rather than traditional absorption pathway can be taken up.\(^{18}\)

In one of the comparative studies, absorption of liposomal ferrous glycinate was higher than ferrous glycinate and that inhibitory effects of phytic acid and zinc on iron absorption were reduced by incorporating ferrous glycinate into liposomes. For example, at the iron concentration of 50 μmol/L, the iron transport at phytic acid concentration of 100, 200, 500, and 1000 μmol/L was decreased by 3.0, 4.6, 7.4, and 14.0% for ferrous glycinate liposomes and by 8.0, 16.5, 27.0, and 45.2% for ferrous glycinate respectively.\(^{18,19}\) Liposomal iron has shown to be significantly more bioavailable than microencapsulated ferric pyrophosphate ingredients and ferrous sulfate in Caco-2 cell model.\(^{16}\)

**CLINICAL USES**

**Chemotherapy-related Anemia**

Anemia in cancer patients is common due to pathologic deficiency in the amount of oxygen-carrying Hb in red blood cells. Current treatment for chemotherapy-associated anemia often relies on the use of erythropoietic-stimulating agents. In one of the recent studies by Mafodda et al,\(^{20}\) a comparison between oral liposomal iron vs IV iron in anemic cancer patients receiving chemotherapy was made. Liposomal oral iron provided similar increase in Hb levels and Hb response, with higher tolerability without the risks or side effects of IV iron. Similarly, from baseline to study end, a mean increase in Hb levels of 2.2 gm/dL and improvement in quality of life (QoL) parameters was noted with liposomal iron in patients with chemotherapy-related anemia.\(^{21}\) Barni et al\(^{22}\) suggest that liposomal iron could be considered as a prophylactic measure to prevent transfusions/erythropoiesis-stimulating agents (ESAs) in cancer patients treated with chemotherapy and preexisting mild anemia.

Liposomal iron can be used as supportive therapy to reduce fatigue and improve QoL in patients with advanced prostate cancer and bone metastasis treated with monthly IV injections. It is also suggested that liposomal iron could be considered for its prophylactic use to prevent transfusion/ESAs in patients with preexisting mild anemia and to improve compliance at treatment with monthly IV injections of Radium-233 dichloride.\(^{23,24}\) In young advanced-stage Hodgkin lymphoma patients, supplementation of oral liposomal iron was well tolerated and maintained Hb above levels, requiring further supportive therapy.\(^{25}\)

**Iron Deficiency Anemia and Inflammatory Bowel Disease**

A preliminary study showed that IDA and IBD patients on liposomal iron (10.5–12.4 gm/dL) had better increase in Hb levels as compared with patients on ferrous sulfate (10.8–11.7 gm/dL) or no iron supplement (11.3–11.9 gm/dL). An increase of Hb >2 gm/dL was more frequent in patients treated with liposomal iron than in patients with no iron supplement. Liposomal iron was well tolerated in both IDA and IBD patients.\(^{26}\) In a similar study, one-third of the IBD patients treated with liposomal iron were normalized in 12 weeks, with an average Hb increase of 11.1 to 11.8 gm/dL (p = 0.0023). Furthermore, the average rating in the questionnaire on QoL of IBD (CCVVEII-9) improved from 61.2 to 66.8 points on the final visit. An adherence of >90% and acceptability of >80% was noted. Therefore, liposomal iron can be helpful in those patients who do not tolerate classic prepared doses of oral iron.\(^{27}\) In refractory anemia, oral liposomal iron is found to be safe, effective, and has demonstrated noninferiority over IV iron.\(^{28,29}\) Compared with conventional iron supplements like ferric ammonium citrate and heme iron, liposomal iron increased iron levels and HB concentrations so as to alleviate the anemia in murine models of sports anemia and anemia of inflammation.\(^{30}\) Liposomal iron was also effective in elderly patients, well tolerated, and produced a great improvement in the anemia condition without side effects, which helped in improving QoL.\(^{31}\) Liposomal iron was found to be more effective than iron sulfate in increasing Hb levels and to reduce inflammatory markers in correction of anemia of chronic inflammatory disease.\(^{32}\) The IBD patients are usually more frequently resistant to oral therapy and they show low compliance. Liposomal iron showed excellent compliance and treatment adherence.\(^{33}\)

**Chronic Kidney Disease-related Anemia**

In the preliminary study, 21 patients with CKD-related anemia were analyzed, 14 of whom were treated with oral liposomal iron and 7 with IV iron. The observed increase of Hb at 8 weeks compared with baseline was similar in both groups, but was significant in the liposomal group only.\(^{14}\) Data show that oral iron administration compared with the IV iron therapy showed a significant increase in terms of Hb concentration and transferrin saturation and a significant decrease regarding C-reactive protein values and weekly consumption of erythropoietin. In conclusion,
liposomal iron seems to be a valid alternative to IV iron therapy in CKD patients. A recent study by Pisani et al showed that oral liposomal iron was a safe and efficacious alternative to IV iron gluconate to correct IDA in nondialysis CKD patients. Oral liposomal iron was also effective in improving and or/maintaining Hb values in hemodialysis patients, normalizing ferritin values and significantly decreasing erythropoietin consumption. According to Griveas, oral liposomal iron seems to be a safe and efficacious alternative in managing CKD patients with anemia.

Other researchers suggest that therapy with two capsules of liposomal iron daily could be an alternative therapy in hemodialysis patients with iron deficiency. Arenas et al showed that liposomal iron was efficacious, well tolerated, and with an excellent therapeutic adherence treatment option for patients with nondialysis CKD. It is documented in one of the studies that addition of liposomal iron to the 12-week standard regimen with subcutaneous erythropoietin is effective in improving hematological parameters but also, more importantly, the QoL with no side effects and excellent tolerability in elderly anemic patients with no end-stage CKD. In anemic CKD patients at stages III to IV, supplementation with liposomal iron was associated with reduced activation of the inflammatory state, as assessed by reduction of erythrocyte sedimentation rate. It is demonstrated that liposomal iron was safe and efficacious in maintaining transferrin saturation levels in peritoneal dialysis patients. Although ferritin levels decreased, they remained within therapeutic range. No gastrointestinal adverse effects were reported.

Celiac Disease

Patients with celiac disease (CD) frequently suffer from IDA and may benefit from iron supplementation. After a follow-up of 90 days, CD and IDA patients in both liposomal and sulfate groups showed an increase in Hb levels compared with baseline (+10.1 and +16.2% for liposomal and sulfate groups respectively), and a significant improvement in all iron parameters, with no statistical difference between the two groups. Therefore, liposomal iron can be effective in providing iron supplementation in difficult-to-treat populations.

Other Conditions

It was demonstrated that liposomal iron was effective in replenishing iron storage in cirrhotic patients and despite the use of a high dose, it is well tolerated. In diabetic patients with IDA supported with liposomal iron, the need for median lispro insulin was lower than that of the patients supported with IV sodium ferrigluconate. Similarly, liposomal iron was found to be safe and cost-effective in hepatitis C virus patients with type II diabetes and anemia due to esophageal or gastric bleeding. In diabetic patients with IDA supported with liposomal iron, the median lispro insulin need appears to be lower than that of the patients supported with IV sodium ferrigluconate. However, the study needs confirmation on a larger cohort of patients.

Researchers assessed the effect of switching to oral liposomal iron in patients receiving IV iron supplementation after bariatric surgery, which currently requires parenteral iron therapy due to intolerance to existing oral products or therapeutic failure. Oral liposomal iron was found to be an excellent alternative to IV iron for maintenance treatment in bariatric surgery patients with iron deficiency. It might help to reduce health care costs and improve the QoL of these patients. Liposomal iron was found to be more effective and well tolerated than iron sulfate for correction of anemia in systemic sclerosis patients who have both chronic inflammation and gastrointestinal malabsorption issues. Liposomal iron therapy was found to be safe, well tolerated, and effective at least as a standard ferrous salt therapy in patients undergoing cytoreductive surgery with intraperitoneal hyperthermic chemotherapy.

COST-EFFECTIVENESS

Scardino et al showed that liposomal iron was able to improve the preoperative protocol, allowing a shorter hospital stay and lower blood transfusions. Thus, liposomal iron supplementation is not only able to produce a faster Hb recovery after surgery, but it is able to decrease surgery-related cost. Simula, in his observation study, noted that in hematological ambulatory practice, oral supplementation with liposomal iron can be effective, safe, and preferred by patients to avoid IV therapy favoring QoL and, last but not least, it has a very low cost for public health. Similarly, liposomal iron was found to prevent the risks and reduce the costs of ESA treatment in elderly cancer patients. Though liposomal iron, compared with other oral formulations, is expensive, the cost of a dose of 30 mg/day of liposomal pyrophosphate iron added to vitamin C 70 mg/day is about 20 times less than the expense that a hospital facility has to face to administer intravenously a 62.5 mg iron gluconate vial. Further, it is suggested by Scarpulla et al that liposomal iron can be considered an efficacious and tolerated alternative for the treatment of mild anemia in IBD patients. The effectiveness of this therapeutic approach is also associated with good compliance.
DOSAGE AND ADMINISTRATION

Liposomal iron is available and the suggested dose is 30 mg/day for 8 to 12 weeks, depending on the conditions.21,26

SAFETY PROFILE

In general, oral supplementation of iron salts is often known to cause nausea, vomiting, epigastric discomfort, sensation of heaviness, and poor gastrointestinal tolerability. However, the distinguishing feature of liposomal iron has been evaluated in several studies and has shown to be devoid of common side effects of conventional oral iron supplementation, such as stomach pain, nausea, constipation, discoloration of the mucous, and feces. Moreover, data show that liposomal iron is better tolerated with few/absence of adverse effects and therefore, patients are more compliant.33

It is reported in the studies that about 30% of patients may experience adverse events with the nonliposomal oral iron, which can lead to dose reduction and/or nonadherence to the prescribed treatment, while adverse events occurred only in 3.1% of subjects on oral liposomal iron.34 In one comparative study, patients on oral liposomal iron had lower drug-related adverse event as compared with IV iron group (3.1% vs 34.5%, p < 0.001). The most commonly experienced adverse events in the liposomal iron group were constipation (4.5%) and diarrhea (4.5%). No serious adverse effects were noted with liposomal iron.35 Similarly, in one of the studies, mild adverse effects like diarrhea, discoloration of stools, and constipation were noted with liposomal iron.36 However, several studies demonstrated no adverse effect of liposomal iron and that it was well tolerated. The distinctive features of liposomal iron like high bioavailability, lesser side effects, and good compliance make it suitable to be used in patients who require iron administration and are intolerant to oral treatment, IV iron treatment, or lack good absorption.

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