Biomedical Science and Clinical Research

Oral Liposomal Iron: A Promising New Strategy for Anemia Management in Clinical Practice

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Abstract
Anemia is a public health problem affecting about a third of the world’s population, the major cause of it being iron deficiency. The many oral iron preparations available at present, are inadequate due to intolerance, or contraindications. IV iron preparations are painful, require patient monitoring and carry the risk of anaphylaxis. Iron salts like Iron pyrophosphate are covered with liposome, a spherical structure of a phospholipidic nature that is similar to those human cell membranes. The 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. Clinical studies showed that oral liposomal iron is a safe and efficacious alternative to correct anaemia, as also it is a viable treatment option for iron deficiency anaemia in pregnant women.

1. Introduction
Iron deficiency and iron deficiency anemia [IDA] are global health problems and common medical conditions seen in daily clinical practice [1]. Recently, up to one-third of the world’s population is suffering from iron deficiency. Infants, the elderly, and women, especially during menstruation and pregnancy, are at high risk for IDA [2]. A schematic summary of the cause and symptoms of iron deficiency anemia is provided in Figure 1.

Oral iron is a first-line therapy to restore iron levels. The limitations with oral therapy include poor iron absorption, and hence low bioavailability, poor tolerability (like abdominal discomfort, nausea/ vomiting, diarrhea, and/or constipation) leading to non-compliance. Iron absorption can be lowered by concomitant intake of dietary phosphates, phytates, and tanates [3].

Figure 1: Iron deficiency anemia causes and symptoms.
In addition to traditional methods, innovative techniques are being developed day by day to enhance iron bioavailability. The aim of this update is to present pharmacotherapeutics of a new formulation of oral liposomal iron.

2. Oral Liposomal Iron
Iron salts like Iron pyrophosphate are covered with liposome, a spherical structure of a phospholipidic nature that is similar to those human cell membranes.

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. Consequently, this method of iron supplementation is associated with high gastrointestinal absorption, high bioavailability, and a low incidence of side effects [4]. 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 [5].

3. Liposomal Iron Therapy in Inflammatory Bowel Disease
Anemia is a clinical condition frequently seen in patients with inflammatory bowel disease (IBD), which is responsible for a significant loss of quality of life. A recent interventional pilot study was conducted from November 2016 to March 2018 in Brazil, to assess the efficacy and safety of using oral liposomal iron to treat iron deficiency anemia in IBD patients [6]. Patients with mild anemia were treated with oral liposomal iron (dose of 28 mg of liposomal iron) for 8 weeks. Treatment response was defined as patients who achieved a haemoglobin (Hb) increase of ≥ 1 g/dL and/or Hb normalization by the 8th week of treatment. Out of 200 screened patients, 40 (20%) had anemia. Of the 21 patients who completed treatment, 13 (62%) responded to oral liposomal iron replacement therapy (mean increases of Hb from 11.4 to 12.6 g/dL). The transferrin saturation index increased by an average of 10.2 (p = 0.006) and the quality of life by 26.3 (p < 0.0001). There was also a mean reduction of 9.2 in...
the perception of fatigue (p < 0.0001). There was a linear correlation between the increase in Hb levels and the improvement of QOL as evaluated by IBDQ (r=0.54; p=0.01; Fig. 4). It was shown that the treatment with oral liposomal iron was effective in improving mild iron deficiency anemia and quality of life, as well as in decreasing fatigue in patients with inactive or mildly active inflammatory bowel disease.

Figure 4: Relationship between hemoglobin levels after treatment with oral liposomal iron and improvement in the perception of quality of life

4. Liposomal Iron in Moderate Chronic Kidney Disease (CKD)
A prospective observational study of patients with stable stage 3 CKD and gastrointestinal intolerance to conventional oral iron therapy was done [7]. An oral 30mg/day dose of liposomal iron was administered for 12 months. 37 patients aged 72.6±14.7 years and with an estimated glomerular filtration rate (eGFR) of 42±10ml/min/1.73m² were included. 32 patients had received previous treatment with conventional oral formulations, 73% of which exhibited gastrointestinal intolerance with treatment adherence of 9.4%. After 6 months with oral liposomal iron, an increase in haemoglobin was observed versus baseline, which was sustained at 12 months. None of the patients experienced adverse reactions that required the treatment to be suspended. Adherence was 100% at both 6 and 12 months.

Iron deficiency is a common cause of anaemia in non-dialysis chronic kidney disease (ND-CKD). This randomized, open-label trial to determine whether liposomal iron, compared with intravenous (IV) iron, improves anaemia in ND-CKD patients was conducted [8]. In this study 99 patients with CKD (stage 3-5, not on dialysis) and iron deficiency anaemia [haemoglobin (Hb) ≤12 g/dL, ferritin ≤100 ng/mL, transferrin saturation ≤25%] were assigned (2:1) to receive oral liposomal iron (30 mg/day, Group OS) or a total dose of 1000 mg of IV iron gluconate (125 mg infused weekly) (Group IV) for 3 months. The study showed that oral liposomal iron is a safe and efficacious alternative to IV iron gluconate to correct anaemia in ND-CKD patients.

6. Liposomal Ferric Pyrophosphate and Ascorbic Acid Supplementation in Pregnant Women with Iron Deficiency Anaemia
This study aimed to determine the effects of liposomal iron pyrophosphate/ascorbic acid on clinical and psychological outcomes in pregnant women [9]. Women at the 11th-13th weeks of gestation with iron deficiency anaemia assuming Sideremil™ (mixture of liposomal iron pyrophosphate and ascorbic acid) from April 2018 to May 2019 were recruited. Results showed significant positive effects on haemoglobin, ferritin, sideremia and transferrin levels, compared to baseline data. A significant improvement of anxiety and depression levels was also observed. Regarding the quality of life, all the domains significantly improved, especially the Physical Role domain. It has been demonstrated conclusively that it is feasible to consider liposomal iron pyrophosphate supplementation as a viable treatment option for iron deficiency anaemia in pregnant women.

7. Dosage and Administration
Liposomal iron is available and the suggested dose is 30 mg/day for 8 to 12 weeks, depending on the conditions [10].

8. Safety Profile Comparisons
Besides its efficacy, oral liposomal iron is well tolerated and the compliance rates are pretty good if compared with other oral iron salts. In fact, it is reported in the literature that over 30% of patients may experience adverse events with the non-liposomal oral iron that can result in dose reduction and/or non-adherence to the prescribed treatment, while adverse events occurred only in 3.1% of the subjects taking oral liposomal iron [11]. The most
commonly experienced adverse events in the studies were constipation (4.5%) and diarrhoea (4.5%). Moreover, the use of oral iron consents to preserve the veins, a very important issue in conservative CKD patients.

9. Pharmacoeconomics of Oral Liposomal Iron

Finally, the costs related to IV formulations administration (like patient admission in the hospital and the necessity of dedicated personnel) and those related to the patient (necessity to move to the hospital, travel expenses, loss of working hours) make this option more expensive than oral iron administration.

10. Conclusion

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.

11. Summary Points

- Oral iron therapy has a poor iron absorption, poor tolerability (like abdominal discomfort, nausea/ vomiting, diarrhea, and/or constipation) leading to noncompliance.
- Techniques are being developed day by day to enhance iron bioavailability.
- Iron salts like Iron pyrophosphate are covered with liposome, a spherical structure of a phospholipidic nature that is similar to those human cell membranes.
- 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.
- 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.
- Liposomal iron has features of high bioavailability, lesser side effects, and good compliance making it suitable to be used in patients who require iron administration and are intolerant to oral treatment, IV iron treatment, or lack good absorption.

References