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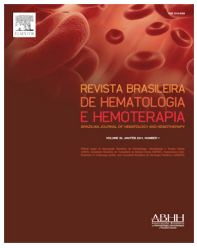

Review article

Intravenous ferric carboxymaltose for the treatment of iron deficiency anemia

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ABSTRACT

Nutritional iron deficiency anemia is the most common deficiency disorder, affecting more than two billion people worldwide. Oral iron supplementation is usually the first choice for the treatment of iron deficiency anemia, but in many conditions, oral iron is less than ideal mainly because of gastrointestinal adverse events and the long course needed to treat the disease and replenish body iron stores. Intravenous iron compounds consist of an iron oxyhydroxide core, which is surrounded by a carbohydrate shell made of polymers such as dextran, sucrose or gluconate. The first iron product for intravenous use was the high molecular weight iron dextran. However, dextran-containing intravenous iron preparations are associated with an elevated risk of anaphylactic reactions, which made physicians reluctant to use intravenous iron for the treatment of iron deficiency anemia over many years. Intravenous ferric carboxymaltose is a stable complex with the advantage of being non-dextran-containing and a very low immunogenic potential and therefore not predisposed to anaphylactic reactions. Its properties permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid session (15-minute infusion) without the requirement of a test dose. The purpose of this review is to discuss some pertinent issues in relation to the history, pharmacology, administration, efficacy, and safety profile of ferric carboxymaltose in the treatment of patients with iron deficiency anemia.

Introduction

Anemia is common. Nutritional iron deficiency anemia (IDA) is recognized as the most common nutritional deficiency disorder in both the developed and developing world, affecting more than two billion people. A 2008 World Health Organization (WHO) report, concentrating on pre-school children and women, estimated that worldwide one in four people were affected by IDA, with pregnant women and preschool-age

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Table 1 – Disadvantages of oral iron therapy.

Gastrointestinal adverse events
Lack of adherence to therapy
Insufficient length of therapy
Limited duodenal absorption due to concomitant gastrointestinal pathology (inflammatory bowel disease or any other cause of chronic inflammation, malignancy)
Long course therapy – 1 to 2 months to resolve anemia and 3 to 6 months to replenish body iron stores

children at the greatest risk.[1] High prevalences of anemia are associated with older age,[2] and with acute and chronic conditions, such as chronic kidney disease.[3]

In a population-based study designed to detect the prevalence of anemia in a healthy population of children (18 months to 7 years) and women (14–30 years) tested in 2006–2007 in the state of Rio Grande do Sul, Brazil, the median prevalence of anemia was 45.4% in 2198 children and 36.4% in 1999 women.[4] The high prevalence of IDA has substantial consequences not only on health but also on subsequent socioeconomic issues, including decreased work capacity and productivity.[1]

Oral iron therapy

Iron has been used to treat anemia for more than 300 years. However, it was not until the 19th century when Pierre Blaud introduced ferrous sulfate that iron therapy became the standard treatment for IDA.[4]

Treatment with oral iron supplements is simple, inexpensive and a relatively effective way of treating iron deficient conditions. If response does not occur within 3–4 weeks of suitable treatment, there is no reason to continue oral iron therapy. Rather, an explanation for failure should be sought. On the other hand, it is very well known that oral iron is a less than ideal treatment. Table 1 shows the main disadvantages of this therapy.

Noncompliance with a prescribed course of oral iron is common, and even in compliant patients, limited intestinal absorption fails to compensate for the iron needs in the presence of ongoing blood losses or inflammatory conditions.[5–7]

In addition, adequate iron stores are essential to achieve maximum benefit from erythropoiesis-stimulating agents (ESAs). Low iron stores and decreased availability of iron are the most common reasons for resistance to the effect of these agents. Thus, oral iron therapy should not be considered for chronic kidney disease (CKD) patients on hemodialysis and cancer patients receiving ESAs because of the inflammatory state. In this scenario, oral iron is poorly absorbed from the intestinal tract due to the upregulation of hepcidin, a peptide hormone that plays a central role in iron homeostasis.[8] In addition, in inflammatory bowel disease (IBD), the possibility that iron may further damage the intestinal mucosa should prompt serious thought about the use of intravenous (IV) rather than oral iron therapy.[9–14]

Intravenous iron therapy

Treatment with IV iron in some clinical situations could present some advantages over oral iron, such as faster and higher increases of hemoglobin (Hb) levels and body iron stores.[15–23]

Table 2 – Clinical indications for intravenous iron therapy.

Post-gastrectomy/bariatric surgery
Anemia of chronic kidney disease
Intestinal malabsorption syndromes
Anemia associated to inflammatory diseases
Inflammatory bowel diseases
Anemia of cancer
Intolerance to oral iron or non-compliance to an oral regimen
Iron-refractory iron deficiency anemias
Hereditary hemorrhagic telangiectasias (Osler-Weber-Rendu disease) and angiodysplasia due to other causes (in cases when oral iron is not tolerated or insufficient for treatment)

For these reasons, modern formulations of IV iron have emerged as a safe and effective alternative for IDA management.[9–14] The main clinical indications for IV iron treatment are listed in Table 2.

Newer intravenous iron formulations

In the last two years, three new IV iron compounds have been released for clinical use in patients with IDA. Two are currently approved for use in Europe (ferric carboxymaltose [FCM],[24–29] and iron isomaltoside 1000 [Monofer®][30] and one in the United States (Ferumoxytol [FeraHeme®]).[31–33]

In their pre-registration trials, all of these three new compounds could potentially have a better safety profile than the more traditional IV preparations, particularly because these products can be given more rapidly and in larger doses than their predecessors. They are promising for the complete replacement of iron within 15–60 min. The use of FCM in Brazil was recently approved by the Brazilian Health Regulatory Agency, *Agência Nacional de Vigilância Sanitária* (ANVISA).

Ferric carboxymaltose

FCM is a parenteral iron dextran-free product and the first of the new agents approved for rapid and high-dose replenishment of depleted iron stores.[24] FCM is an iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell. The design of the macromolecular ferric hydroxide carbohydrate complex allows controlled delivery of iron to the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of large amounts of ionic iron being released into the serum.[24]

FCM is a stable complex with the advantage of being non-dextran-containing and having a very low immunogenic potential and therefore not predisposed to high risk of anaphylactic reactions. Its properties permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid session (15-minute infusion) without the requirement of a test dose.[25–28]