European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 480–491

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer®), a new intravenous iron preparation and its clinical implications

Markus R. Jahn [a], Hans B. Andreasen [b], Sören Fütterer [a], Thomas Nawroth [a], Volker Schünemann [c], Ute Kolb [d], Wolfgang Hofmeister [e], Manuel Muñoz [f], Klaus Bock [g], Morten Meldal [g], Peter Langguth [a,*]

[a] Institute of Pharmacy and Biochemistry, Johannes-Gutenberg University, Mainz, Germany
[b] Pharmacosmos A/S, Holbaek, Denmark
[c] Department of Physics, Technical University Kaiserslautern, Kaiserslautern, Germany
[d] Institute of Physical Chemistry, Johannes-Gutenberg University, Mainz, Germany
[e] Institute of Geosciences, Johannes-Gutenberg University, Mainz, Germany
[f] Transfusion Medicine, School of Medicine, University of Málaga, Málaga, Spain
[g] Carlsberg Laboratory, Gamle Carlsberg Vej 10, Valby, Denmark

ARTICLE INFO

Article history:
Received 14 December 2010
Accepted in revised form 15 March 2011
Available online 23 March 2011

Keywords:
Inorganic nanoparticles
Colloids
Stability
Free iron
Iron supplementation
Release rate

ABSTRACT

The treatment of iron deficiency anemia with polynuclear iron formulations is an established therapy in patients with chronic kidney disease but also in other disease areas like gastroenterology, cardiology, oncology, pre/post operatively and obstetrics' and gynecology. Parenteral iron formulations represent colloidal systems in the lower nanometer size range which have traditionally been shown to consist of an iron core surrounded by a carbohydrate shell. In this publication, we for the first time describe the novel matrix structure of iron isomaltoside 1000 which differs from the traditional picture of an iron core surrounded by a carbohydrate. Despite some structural similarities between the different iron formulations, the products differ significantly in their physicochemical properties such as particle size, zeta potential, free and labile iron content, and release of iron in serum. This study compares the physiochemical properties of iron isomaltoside 1000 (Monofer®) with the currently available intravenous iron preparations and relates them to their biopharmaceutical properties and their approved clinical applications. The investigated products encompass low molecular weight iron dextran (CosmoFer®), sodium ferric gluconate (Ferrlecit®), iron sucrose (Venofer®), iron carboxymaltose (Ferinject®/Injectafer®), and ferumoxytol (Feraheme®) which are compared to iron isomaltoside 1000 (Monofer®). It is shown that significant and clinically relevant differences exist between sodium ferric gluconate and iron sucrose as labile iron formulations and iron dextran, iron carboxymaltose, ferumoxytol, and iron isomaltoside 1000 as stable polynuclear formulations. The differences exist in terms of their immunogenic potential, safety, and convenience of use, the latter being expressed by the opportunity for high single-dose administration and short infusion times. Monofer is a new parenteral iron product with a very low immunogenic potential and a very low content of labile and free iron. This enables Monofer, as the only IV iron formulation, to be administered as a rapid high dose infusion in doses exceeding 1000 mg without the application of a test dose. This offers considerable dose flexibility, including the possibility of providing full iron repletion in a single infusion (one-dose iron repletion).

1. Introduction

Parenteral iron therapy is today widely used for the treatment of iron deficiency anemia. Patients with chronic kidney disease (CKD) also frequently need treatment with parenteral iron preparations in addition to erythropoietin stimulating agents [1]. For renal failure patients on dialysis, the average iron requirements due to blood loss are equivalent to 1–3 g of elemental iron per year [2]. This can easily be accomplished by frequent low dose IV iron administrations, during the regular dialysis sessions.

From initial, generalized use in nephrology parenteral iron therapy has spread in recent years to other disease areas; gastroenterology [3], cardiology [4,5], oncology [6], pre/post operatively [7], obstetrics', and gynecology [8]. However, care providers in these segments have less frequent patient contact, resulting in an increased demand for convenient administration of large IV iron doses in one clinical session.

* Corresponding author. Institute of Pharmacy and Biochemistry, Pharmaceutical Technology and Biopharmaceutics, Johannes-Gutenberg University Mainz, D-55099 Mainz, Germany.Tel.: +4961313925746; fax: +49 6131 3925021.
E-mail address: langguth@uni-mainz.de (P. Langguth).

0939-6411/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2011.03.016

Historically, the first parenteral iron preparations were toxic, being administered as an iron oxyhydroxide complex. This problem was circumvented with the introduction of compounds containing iron in a core surrounded by a carbohydrate shell [9]. The currently marketed parenteral iron preparations are considered equally efficacious but vary in molecular size, pharmacokinetics, and adverse reaction profiles. The intravenous iron agents currently available include high molecular weight iron dextran (Dexferrum®), low molecular weight iron dextran (Cosmofer®, Infed®), sodium ferric gluconate (Ferrlecit®), iron sucrose (Venofer®), iron carboxymaltose (Ferinject®/Injectafer®), and ferumoxytol (Feraheme®). High molecular weight iron dextran has been linked to an increased risk of anaphylaxis and anaphylactoid reactions, and it is not available in Europe [10–13]. Although this problem is very much reduced with low molecular weight iron dextran [10–13], there is still a test dose requirement and the infusion of larger doses is hampered by a 4–6 h infusion time. Sodium ferric gluconate and iron sucrose can only be used in moderate iron doses due to the relative weakness of the iron complex [14]. Two new parenteral iron compounds, iron carboxymaltose, and ferumoxytol were recently introduced in the EU and the US markets, respectively. The FDA failed to approve iron carboxymaltose for distribution in the USA due to unexplained hypophosphatemia, an increased number of adverse cardiac events and an imbalance in death rates in the treatment arm compared to the control arm in different RCTs [15].

Although more stable than sodium ferric gluconate and iron sucrose, the administration of iron carboxymaltose and ferumoxytol is still limited to a maximum total dose of 1000 mg and 510 mg, respectively.

The newest IV iron agent Iron isomaltoside 1000 (Monofer®) (e.g., iron oligo isomaltoside (1000) as generic name) is developed and manufactured by Pharmacosmos in Denmark and was introduced in Europe in 2010. The carbohydrate isomaltoside 1000 is a pure linear chemical structure of repeating α1-6 linked glucose units, with an average size of 5.2 glucose units and an average molecular weight of 1000 Da, respectively. It is a nonbranched, nonanaphylactic carbohydrate [16,17], structurally different from branched polysaccharides used in iron dextran (Cosmofer).

The production method and the short nonionic isomaltoside 1000 allows for the construction of a special matrix-like structure with interchanging iron molecules and linear isomaltoside 1000 oligomers. The resulting matrix contains about 10 iron molecules per one isomaltoside pentamer in a strongly bound structure that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron toxicity [18,19]. This allows iron isomaltoside 1000 to be administered safely as a rapid high dose intravenous infusion or bolus injection offering considerable dose flexibility, including the possibility of providing full iron repletion in a single infusion, the so-called one-dose iron repletion.

This article introduces and compares physicochemical properties of iron isomaltoside 1000 (Monofer®) with currently marketed iron formulations. In addition, this comparative study of polynuclear iron formulations currently used in the treatment of anemic disorders includes perspectives on the relevance of these properties with respect to safety, efficacy, and convenience of administration.

2. Materials and methods

2.1. Materials

Sodium ferric gluconate (Ferrlecit®, 12.5 mg Fe/mL in 3.2 mL ampoules; Sanofi-Aventis, Frankfurt, Germany), iron sucrose (Venofer®, 20 mg Fe/mL in 5 mL ampoules; Vifor, München, Germany), low molecular weight iron dextran (CosmoFer®, 50 mg Fe/mL in 2 mL ampoules; Teva, Mörfelden-Walldorf, Germany), iron isomaltoside 1000 (Monofer®, 100 mg Fe/mL in vials; Pharmacosmos, Holbaek, Denmark), iron carboxymaltose (Ferinject®, 50 mg Fe/mL in 2 mL vials; Vifor, München, Germany), and ferumoxytol (Feraheme®, 30 mg Fe/mL, in 17 mL vials; AMAG Pharmaceuticals, Lexington, MA, USA) were obtained from a pharmacy or directly from the manufacturer. The Ferrozine® reaction kit was purchased from Roche Diagnostics GmbH, Mannheim. All iron formulations were used immediately after opening the vial or kept at 4 °C under nitrogen. Solutions were made from double-distilled water.

2.2. Gel permeation chromatography (GPC)

The apparent average molecular weight was analyzed by gel permeation chromatography. Prior to sample analysis, the columns were calibrated using dextran standards. The dextran standards used for GPC calibration were the commercial available Pharmacosmos standards and consisted of Dextran 25, 50, 80, 150, 270, and 410, respectively. The average molecular weights M_w and the peak average molecular weights M_P were 23.000, 21.400; 48.600, 43.500; 80.900, 66.700; 147.600, 123.600; 273.000, 196.300; 409.800, 276.500 for Dextran 25, 50, 80, 150, 270, and 410, respectively. The standards have been evaluated against the Ph.EUR and USP dextran standards.

The detector used in the GPC measurements is a VE 3580 RI detector (Viscotec). Data are collected and calculations are made using the Omnisec 4.1 software from Viscotec.

The hydrodynamic diameter d_h was calculated from the hydrodynamic volume $V_h = M_p \cdot |\eta|$, where the intrinsic viscosity $|\eta|$ is given by the Mark Houwink equation [20]

$$|\eta| = k\overline{M}_v^a$$

where $\overline{M}_v^a$ is the viscosity average molecular weight.

2.3. Dynamic light scattering (DLS) and zeta potential

The size distribution and zeta potential of the whole particle, which can include an iron hydroxide core plus a carbohydrate shell, was determined by DLS. The diluted samples (0.4 mg Fe/mL double-distilled and sterile filtered water) were measured using a Zetasizer Nano S (Malvern Instruments Ltd.; Worcestershire, UK) including a He–Ne Laser with a wavelength of $\lambda = 633$ nm, which illuminated the samples and detects the scattering information at an angle of 173° (Noninvasive Back-scatter technology). Zeta potential measurements were performed at different pH values by addition of 0.1 N HCl or NaOH, respectively. The data were analyzed with the firmware, Zetasizer Software DTSv612 yielding volume distribution data.

2.4. Transmission electron microscopy (TEM)

The dimension of the iron complex nanoparticle core was determined with an EM420 transmission electron microscope (FEI/Philips, Oregon, USA) at 120 kV. All preparations (1 mg Fe/mL, double-distilled water) were deposited onto a hydrophilized copper grid (300 mesh, Ø 3 mm) and were allowed to dry. The median of the geometrical diameter $d_g = \sqrt{(d_s^2 + d_l^2)/2}$ was determined ($n = 50$, d_s = shortest dimension, d_l = longest dimension).

2.5. X-ray diffraction (XRD)

X-ray measurements of dried out solutions (30 °C) were performed with a XRD 3000 TT (Seifert, Ahrensburg, Germany) using Cu radiation ($\lambda = 1{,}54178$ Å, 40 kV, 30 mA) in Bragg Brentano configuration (automatic divergence slit, angular rate 0,18°/min).