Journal of Trace Elements in Medicine and Biology 26 (2012) 127–130

Contents lists available at SciVerse ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.de/jtemb

Iron mobilization using chelation and phlebotomy☆

Trond Peder Flaten[a,*], Jan Aaseth[b], Ole Andersen[c], George J. Kontoghiorghes[d]

[a] Department of Chemistry, Norwegian University of Science and Technology, NO-7491 Trondheim, Norway
[b] Innlandet Hospital Trust, Kongsvinger Hospital Division, NO-2226 Kongsvinger, Norway
[c] Department of Science, Systems and Models, Roskilde University, P.O. Box 260, DK-4000 Roskilde, Denmark
[d] Postgraduate Research Institute of Science, Technology, Environment and Medicine, 3, Ammochostou Street, Limassol 3021, Cyprus

ARTICLE INFO

Keywords:
Iron overload disorders
Haemochromatosis
Thalassaemia
Chelation
Deferiprone (L1)
Deferoxamine (DFOA)
Deferasirox

ABSTRACT

Knowledge of the basic mechanisms involved in iron metabolism has increased greatly in recent years, improving our ability to deal with the huge global public health problems of iron deficiency and overload. Several million people worldwide suffer iron overload with serious clinical implications. Iron overload has many different causes, both genetic and environmental. The two most common iron overload disorders are hereditary haemochromatosis and transfusional siderosis, which occurs in thalassaemias and other refractory anaemias. The two most important treatment options for iron overload are phlebotomy and chelation. Phlebotomy is the initial treatment of choice in haemochromatosis, while chelation is a mainstay in the treatment of transfusional siderosis. The classical iron chelator is deferoxamine (Desferal), but due to poor gastrointestinal absorption it has to be administered intravenously or subcutaneously, mostly on a daily basis. Thus, there is an obvious need to find and develop new effective iron chelators for oral use. In later years, particularly two such oral iron chelators have shown promise and have been approved for clinical use, namely deferiprone (Ferriprox) and deferasirox (Exjade). Combined subcutaneous (deferoxamine) and oral (deferiprone) treatment seems to hold particular promise.

Introduction

Iron is essential for all living organisms, but in humans, there are no regulatory mechanisms for iron excretion. Thus, the body iron burden is mainly controlled by regulatory mechanisms for absorption from the gut [1]. A common cause of pathological deposition of iron is the autosomal recessive inherited disease HFE-related haemochromatosis, a form of primary iron loading disease which is characterized by dysregulated iron absorption leading to progressive deposition and pathology of the liver with subsequent involvement of various other organs [2]. The key treatment for primary haemochromatosis is phlebotomy.

Another form of excessive iron deposition is transfusional siderosis. Patients with severe anaemias, including patients where the anaemia is due to ineffective erythropoiesis (mainly β-thalassaemia and sickle cell disease), are treated with repetitive blood transfusions. In such patients, iron overload often results, necessitating iron chelation therapy. These patients represent a huge global public health problem [3].

The main aim of the present brief overview is to outline the current knowledge of iron mobilization, with emphasis on chelation therapy, including combined chelation using deferoxamine (desferrioxamine, Desferal, DFOA) and deferiprone (L1). The main research needs in this field are to further clarify molecular mechanisms of disease progression and to develop new chelators that are more effective and less toxic than those presently available.

Haemochromatosis and phlebotomy

The autosomal recessive disease known as *primary* haemochromatosis, or *hereditary* haemochromatosis, is usually transferred by a gene mutation on the short arm of chromosome 6 (the *HFE* gene, which is linked to the HLA locus), in northwest Europe most often the C282Y mutation [4]. In populations of northern European origin, the prevalence of C282Y mutation homozygosity can be as high as 0.5% [5,6] or even higher [7], making primary haemochromatosis probably the most common genetic disorder in Caucasians. There are several forms of primary haemochromatosis, most of which are inherited in an autosomal recessive manner [1,8]. HFE-related haemochromatosis is the commonest form. The *HFE* mutations lead to deficiency in the hepatic peptide hormone hepcidin, which is currently considered to be the principal regulator of iron absorption and its tissue distribution [9].

The symptoms of primary haemochromatosis are caused by progressive iron deposition. The first clinical symptoms may become apparent during the 3rd to 6th decade of life, men usually

☆ Paper presented at the IX ISTERH conference, October 2011.
* Corresponding author.
E-mail address: trond.flaten@chem.ntnu.no (T.P. Flaten).

0946-672X/$ – see front matter © 2012 Elsevier GmbH. All rights reserved.
http://dx.doi.org/10.1016/j.jtemb.2012.03.009

being affected earlier than menstruating women. An unspecific asthenia may be present before other early symptoms such as arthropathy. The arthropathy of haemochromatosis resembles the osteoarthritic changes observed in calcium pyrophosphate deposition [10]. Involvement of the metacarpophalangeal joints is a hallmark of the arthropathy of haemochromatosis [11]. Other joints may be involved [11], often the joints in the ankle or foot [12]. Other clinical manifestations of primary haemochromatosis include hepatomegaly, skin pigmentation, diabetes mellitus, hypopituitarism, hypogonadism, impotence, heart failure, liver cirrhosis and hepatocellular carcinoma [13]. Clinical symptoms rarely occur before the total body burden of iron exceeds 15 g, compared to a level below 5 g in healthy human adults. Primary haemochromatosis should be suspected in any case with serum ferritin values above 200 μg/l if the transferrin saturation is 50% or higher, even in the absence of clinical symptoms. Then, genetic testing should be carried out.

Phlebotomy is the metal depletion treatment of choice in primary haemochromatosis [14,15], markedly improving survival and preventing most of the complications [13]. This approach involves removal of 450–500 ml blood once a week until serum ferritin is reduced to about 50 μg/l, after which one venesection every three months usually will be sufficient. The body burden of iron can be reduced by maximally 10–15 g during one year by using weekly phlebotomies. Some patients, however, apparently have body stores above 20–25 g of iron. For patients in whom extensive iron depots need to be mobilised rapidly, combined treatment with phlebotomy and an iron chelating agent may be a clinical option. An obvious candidate for chelation would be DFOA. An adjuvant therapy to phlebotomy may be erythropoietin, which has been reported to accelerate the mobilization of tissue iron into the red blood cells [16].

Transfusional siderosis and chelation therapy

Transfusional siderosis is frequently seen in patients with severe chronic anaemias, chiefly those with β-thalassaemia or sickle cell disease, who need treatment with repetitive blood transfusions [2,17]. However, the treatment in such patients is a double-edged sword – each unit of transfused blood contains 200 mg of iron and because the body has no mechanism to excrete excess iron, chronic iron overload often results, causing damage to the liver, heart, endocrine organs, and other tissues. Obviously, phlebotomy cannot be used to treat iron overload in transfusional siderosis induced in patients with thalassaemia major and other refractory anaemias. Such patients must be treated by iron chelation therapy [18], which has played a vital role in the management of these patients since the introduction of the parenterally administered chelator DFOA more than 50 years ago. Iron chelation therapy has been extensively used especially in thalassaemia major patients, but also in some other haemoglobinopathies such as sickle cell anaemia [19,20]. This disease group is characterized by structural changes of the haemoglobin molecule, which leads to many abnormalities including ineffective transport of oxygen to the tissues and reduced half-life of the red cells [21].

Chronic hereditary anaemias are still rare in North European countries, with only about 60 transfusion-requiring cases in Norway and Sweden, mostly children of foreign origin [22]. The different thalassaemias are much more frequent in the Mediterranean and other countries where malaria was formerly endemic. Since the different thalassaemias result in varying degree of resistance to the malaria parasite, there has been a positive selection pressure for individuals carrying these mutations [23]. The sickle cell gene is very frequent in equatorial African populations because heterozygotes are protected from severe consequences of malaria. The gene frequencies in different areas are apparently related to the frequency and severity of malaria episodes [24].

The WHO estimates that about 7% of the population world-wide are carriers of a haemoglobinopathy. Thus, this diverse group of diseases is probably the most common hereditary errors in the world.

About 400,000 children are born yearly with a severe haemoglobinopathy including thalassaemia major [25]. Serious anaemic cases such as thalassaemia major usually require transfusions every two to four weeks. There exists no consensus as to the follow-up and therapy of the resulting iatrogenic siderosis. Most of the patients will rapidly get a ferritin value above 2000 μg/l. Combined chelation therapy with DFOA and L1 is often used in Scandinavia [22].

The traditional iron chelator, DFOA, is poorly absorbed in the gastrointestinal tract and must therefore be administered by intravenous infusion or painful subcutaneous infusion, compromising compliance in many patients [26,27]. Its distribution volume is mostly extracellular. The protein binding in plasma is low, less than 10%. Its renal excretion is biphasic with the slow half-life being about 6 h. The acute toxicity is rather low, and intravenous infusion is relatively safe if care is taken not to administer the dose rapidly, which can result in hypotension. However, a wide range of side effects have been noted during continued use in iron overload patients including ophthalmic and auditory toxicity, bacterial and fungal infections, changes in blood histology, allergic and skin reactions, and pulmonary, renal and neurological effects [28]. A problem of DFOA treatment is that it is rather expensive. Only 10–50 mg iron can be removed by one single treatment, and weekly in-clinic parenteral DFOA administrations extended for a period of one year removed only about 4 g of iron [29].

The recommended DFOA protocol involves the subcutaneous use of 40–60 mg/kg/day, 8–12 h/day for a minimum 5 days per week [19]. Obviously, such treatment is very stressful to patients and there is high rate of non-compliance. Therefore, the need for more efficient, effective and non-toxic iron chelation therapy resulted in the development of orally effective iron chelators.

The first orally active chelating agent to be developed was L1 or deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one), which was approved in India in 1995, by the EU regulatory authorities in 1999, and in the USA in 2011. More than 7500 patients were treated with deferiprone by 2003 [30]. L1 offers an alternative to DFOA in the treatment of transfusional iron overload in thalassaemia, due to its low price compared to DFOA, the possibility of continued treatment of patients not tolerating DFOA, and because it can be administered orally. The acute toxicity of L1 is somewhat lower than that of DFOA. The present clinical experience indicates some side effects including gastric discomfort, zinc depletion, transient agranulocytosis or transient musculoskeletal and joint pain. Some patients suffering side effects have received continued treatment with lower, more frequent doses [31]. The recommended dose is 75–100 mg/kg/day administered as 250 mg capsules or tablets with about 8-h intervals. Since leukopenia is a possible side effect, leukocyte counts are recommended weekly.

Deferiprone is rapidly absorbed in the gastrointestinal tract and normally appears in serum a few minutes after oral administration. It is only partly metabolized in the liver. The main excretion route is the kidneys, with a half-life of 47–134 min [32,33]. The recovery from urine is close to 100%; the main species are free L1, the Fe and Cu complexes and the glucuronide. Deferiprone is a bidentate iron chelator forming a 3:1 complex with iron, and it is likely to act intracellularly [34].

Combined DFOA and L1 chelation at lower than the normal clinical doses has been reported to efficiently remove iron from thalassaemic patients [35,36], indicating a potentially important improvement in iron chelation. The advantages of combined