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Iron chelating agents in clinical practice

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Abstract

The relevance of iron chelators in medicine has increased in recent years. Iron is essential for life but it is also potentially more toxic than other trace elements. This is due to the lack of effective means to protect human cells against iron overload and to the role of iron in the generation of free radicals. To protect patients from the consequences of iron toxicity, iron chelating agents have been introduced in clinical practice. Unfortunately, the ideal chelator for treating iron overload in humans has not been identified yet. The aim of this review is to report the experience with desferrioxamine therapy in patients affected by β-thalassemia major according to: bioavailability; mechanism of interactions with hepatocellular iron:

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release of iron chelates and their excretion; impact of iron chelation on survival in thalassemia patients and side effects of prolonged therapy. Problems related to the development of non-toxic oral iron chelators are also discussed, with particular emphasis on the preliminary data on usefulness and safety of deferiprone (L1), recently evaluated in different clinical trials. Iron chelating therapy has been introduced, in recent years, even in the therapy of disorders not characterized by iron overload. Here the following new therapeutic indications are discussed: adult respiratory distress syndrome, myocardial ischemia, cancer and malaria.

Keywords: Iron-chelators; Desferrioxamine; Deferiprone; Thalassemia

1. Introduction

Iron chelators are used in medicine to protect patients from the consequences of iron overload and iron toxicity in organs and tissues. The ideal chelator for treating iron overload in humans should act as a selective depletor of iron, should be efficiently absorbed by the gastrointestinal tract, could not cross the blood–brain and placental barriers and should lack or have a low toxicity. Such a chelating agent has not been identified yet and this goal is at the basis of multiple research projects in this field. In this review, the experience with long-term iron chelating therapy in patients affected by chronic transfusion-dependent anemias will be summarized with particular emphasis on thalassemic patients who are the main target of iron-chelating drugs. The experience in thalassemia patients with the well established chelator desferrioxamine and with the orally active deferiprone will be outlined. This review is also intended to report the most recent development of new non-toxic and orally effective iron chelating agents and their possible application in clinical use. New indications for iron chelating therapy will also be explored, such as the use of iron chelation in oncology to prevent tumor cell growth by the inhibition of iron-dependent enzymes, the application of iron-chelating agents in the therapy of infectious disease with particular emphasis on their action as antimalarials, the experience of iron-chelating drugs in the therapy of adult respiratory distress syndrome and in the therapy of myocardial ischemia. Finally, the relevance of the dialogue among clinicians, pathologists, pharmacologists, biochemists, chemists, molecular biologists and other experts in metal toxicity in order to improve our knowledge on the relationship between the metabolism of iron and other trace elements will be discussed. This implies the final goal of prolonging survival and improving the quality of life of iron-loaded patients.

2. Iron overload and toxicity

Iron is essential for life: all living cells, whether prokaryotic or eukaryotic, need a supply of iron for reduction of oxygen (respiration), reduction of carbon dioxide

(photosynthesis), reduction of dinitrogen or other fundamental biological processes [1]. Excessive amounts of iron may become very toxic to the human body and, eventually, is fatal for vital cell structures [2].

Iron overload may be defined as an excess in total body iron stores. The normal iron concentration in the human body ranges between 40 and 50 mg/kg of body weight [3]. Most of this iron is present in hemoglobin and in myoglobin: all the rest is stored as ferritin or as its less accessible form, hemosiderin. Only a few hundred milligrams of iron are stored in enzymes such as cytochrome *c* oxidase which, however, are essential to human life [1]. Humans have very limited capacity for excretion of excess iron: in particular they lack any effective means to protect cells and tissues against iron overload. As a consequence, any increase in iron intake may cause in a short time an increase in body iron stores [4]. Iron balance is normally regulated by controlling iron absorption in the proximal small intestine [5]. In women, losing iron in the menstrual cycle could protect against excess iron toxicity and it is considered to be, at least in part, responsible for their greater longevity than men [1]. The major regulators of mucosal iron absorption are the amount of body iron stores and the level of erythropoiesis [6]. Iron overload may be caused by two different factors:

1. parenteral administration of iron, as in chronic transfusion therapy;
2. increase in iron absorption from the diet, that may be genetically determined like in hereditary hemochromatosis [7] or caused by dietary iron overload [8].

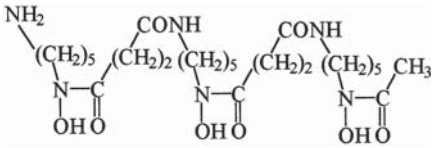
When the accumulation of iron in organs exceeds the body capacity for safe storage, potentially lethal tissue damage results [9]. The severity of iron toxicity seems to be related to the amount of body iron burden. Recent studies in patients with thalassemia major found that the magnitude of the body iron burden was the major determinant of the risk of clinical complications and of early death [10,11]. Target organs for iron-induced injury are the liver, pancreas and heart [12].

In the category of patients affected by chronic anaemia, who need regular blood transfusions in order to sustain their normal growth and development during childhood, β-thalassemia major (BTM) constitutes one of the most serious public health problems in the Mediterranean area [13], in the Middle East, in the Indian subcontinent, in Southeast Asia [14] and, in particular, in the island of Sardinia [15]. BTM is an autosomal recessive disease, characterized by absent or decreased synthesis of the β globin gene: the number of thalassemic children requiring regular blood transfusions and a program of iron chelation has been estimated to be 100 000 world-wide. In patients with thalassemia major, iron contained in transfused red cells inexorably accumulates if a concomitant regular chelation therapy is not programmed [16]. The major pathological manifestations observed in patients with BTM are related to iron overload: chronic liver disease, characterized by hepatocytic and Kupffer cell iron storage, fibrosis and, eventually, cirrhosis [17,18]; dilatative cardiomyopathy with congestive heart failure is nowadays the most common cause of death in patients affected by BTM who reach adolescence and adulthood [19,20]. Even cardiomyopathy is related to cardiac hemosiderosis: a preferential accumulation of iron in the interventricular septum and in the left ventricle wall has been observed [21]. The toxic effects of iron overload has been

demonstrated in cultured heart cells: incubation of rat heart cell cultures with iron concentrations from 20 up to 80 g/ml resulted in a marked decrease in amplitude and rate of contractions and in gross abnormality in rhythmicity [22].

3. Desferrioxamine

Desferrioxamine is the only chelating agent to have been extensively used in clinical practice [23] after its discovery more than 30 years ago. It is a siderophore produced by *Streptomyces pilosus* [24], discovered by the team of Prelog and his co-workers Zahner and Keberle.



Desferrioxamine, earlier recognized as an antagonist of the antibiotic ferrimycin, was successively identified as an iron chelating agent [25]. It is a trihydroxamic acid with three residues of 1-amino-5-*N*-hydroxy aminopentane, two of succinic acid and one of acetic acid organized in a linear array; the free amino group explains its very high water solubility. Although it has been synthesized the use of the natural product is more economic.

Initially used in the therapy of acute iron poisoning [26], desferrioxamine was later introduced in thalassemia treatment, giving a fresh chance to more than 100 000 thalassemic patients requiring iron chelating therapy. The widespread use of desferrioxamine was firmly established, thanks to British investigators such as Berry, Modell, Pippard and Hoffman and to Italian clinicians such as Cao. The relevance of desferrioxamine in clinical practice and its role in the progress of the therapy of thalassemia patients has been underlined on the occasion of the 1991 Pharmaceutical of the Year price, awarded to desferrioxamine by the Munchener Medizinische Wochenschrift [27]. In order to better understand the value of this award, it is useful to observe that it had been previously given to aspirin, cortisone and penicillin. Desferrioxamine is the only iron-chelating agent approved for clinical use [28]. In the following, we shall focus on

- the bioavailability;
- the mechanism whereby it interacts with hepatocellular iron, with iron stored in macrophages and with iron in transit;
- the release of its iron chelates and their subsequent biliary or urinary excretion;
- the impact of iron chelation on survival in thalassemia patients;
- the side effects of prolonged therapy.

Bioavailability is defined by Hider [29] as the percentage of absorbed dose of a drug which reaches the systemic blood circulation. It depends on the absorption of the drug from the gastrointestinal tract and from the extraction by hepatocytes from the portal blood supply. Low or high bioavailability may be requested in iron chelators, depending on the clinical setting and on the main target of chelating

therapy. Thus, when a general systemic action of a chelator is required, a high bioavailability is ideal. On the contrary, when liver is the target of iron chelation, an efficient absorption of the chelator by hepatocytes and, consequently, a low bioavailability is ideal. Two major factors influence the absorption of iron chelators from the gastrointestinal tract: the oil/water distribution coefficient [30] and the molecular weight. To achieve 70% absorption of an iron chelator, its molecular weight [31] needs to be < 300. A 70% absorption of the dose is mandatory for iron chelators: 50% absorption could leave in the lumen such a level of the chelator that might disturb the microbiological flora [29]. Most siderophores, including desferrioxamine, have a molecular weight from 500 to 900 Da which effectively excludes hexadentate ligands, such as desferrioxamine, from consideration as orally active chelators. In contrast deferiprone and 1,2-diethyl-3-hydroxy-4-pyridinone, two ligands of molecular weight 139 and 167 Da, respectively, are both efficiently absorbed in man [32]. Since desferrioxamine given orally is poorly absorbed, to be effective it must be administered subcutaneously [33], intramuscularly [34] or by intravenous infusion with a small portable syringe pump, ideally for 9–12 h each day [35]. This difficult regimen of desferrioxamine parenteral treatment easily explains why only part of thalassemic patients comply with iron chelating therapy, in spite of the knowledge that the advent of treatment with desferrioxamine has changed the gloomy prognosis of thalassemia patients [36]. On entering blood by intravenous injection, desferrioxamine plasma clearance [37] is generally considered rapid, with half life of 5 to 10 min, also if a longer half life (3.05 ± 1.30 h) has been estimated in a recent study [38]. While only a small part of desferrioxamine is inactivated within human plasma, the major part undergoes uptake by hepatocytes. The rapid loss of circulating activity of desferrioxamine after intravenous injection is the main reason why prolonged infusion results in more efficient iron chelation [39]. After injection of desferrioxamine, both fecal and urinary iron excretion are observed. Probably the two excretion pathways reflect two different actions of the drug. Fecal excretion could only arise through iron chelation within the hepatocytes, followed by excretion in the bile of the iron–desferrioxamine complex [39]. The source of urinary iron remains more controversial: urinary excretion could derive from iron chelation within Kupffer cells and within other monophagocytic cells like spleen macrophages [40,41]. A further source to the urine is likely to be any nontransferrin bound iron in plasma of patients with a fully saturated plasma trasferrin, this kind of iron is reduced by desferrioxamine treatment [42]. The picture emerges that the major source of iron excreted through faeces by desferrioxamine is iron within hepatocytes, while urinary excretion could reflect an additional pathway of chelation, predominantly extracellular, regarding plasma nontransferrin bound iron, membrane-related iron of hepatocytes and iron in macrophages [39]. The mechanism by which desferrioxamine is effective in removing intra and extracellular iron is not yet completely understood. To further the understanding of how desferrioxamine, as well other chelators, exert their effects on cells, many animal [43] and cellular models [44] have been proposed. Experiments on hepatocytes have shown that the hepatocyte plasma membrane possesses a number of facilitated transport processes which are particularly efficient for the absorption of

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