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An overview of complications associated with deferoxamine therapy in thalassemia

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ABSTRACT

Thalassemic syndromes are the most common genetic diseases in the world that are related to blood transfusion and iron overload in the body. In β -thalassemia major multiple blood transfusions due to ineffective erythropoiesis lead to iron excess in the body. Iron chelating agent deferoxamine is used to treat chronic iron overload in patients with β -thalassemia in an attempt to reduce morbidity and mortality related to deposition of excess iron in body tissue. However, a very short half-time, the need of repetitive injections and non-specialized distribution in tissues can lead to side effects, such as ophthalmic and renal complications, neurological, skeletal changes and hearing loss, headaches, and infection too. Patients should be monitored periodically for complications. The risk of toxic effects in doses of more than 50 mg/kg/d is higher. Keeping deferoxamine therapeutic index can avoid drug overdose and side effects.

Implication for health policy/practice/research/medical education:

Deferoxamine is used to treat chronic iron overload in patients with β -thalassemia. Short half-time of deferoxamine and the need of repetitive injections can lead to side effects. Patients should be monitored periodically for complications. Keeping deferoxamine therapeutic index can avoid drug overdose and side effects.

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Beta-thalassemia major is a homozygous form of β -thalassemia and is a chronic microcytic anemia caused by a mutation in the beta-globulin gene which leads to a deficit in hemoglobin production, early destruction of red blood cells and frequently blood transfusion and increased iron load consequently in patients. This extra iron causes irreversible damage to the organs' body by causing oxidative stress which can lead to heart failure, liver cirrhosis, endocrine problems such as hypothyroidism, hypogonadism and growth problems, and even neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Iron chelating drugs are needed to reduce iron load. These drugs are available in injectable and oral forms (1). Deferoxamine is the first drug to be used to treat acute iron poisoning and chronic iron overload in people with chronic blood transfusions. The drug after

entering the cell binds with the iron, forms a complex called Ferrioxamine, which is easily disintegrated in the body and excreted in urine and stool (2, 3). Deferoxamine has doubled the patient's life expectancy. In chronic iron overload, long-term use of this medication reduces the accumulation of iron in the liver and reduces the risk of hepatic fibrosis (4). One of the positive effects of this drug on the endocrine system is a reduction in insulin resistance. Deferoxamine improves, FBS and HbA1c and also B-cell function (5). The chelators that have been approved for treatment have some specific side effects due to the non-targeted distribution in the body. It should be considered that iron is essential for metabolic activities therefore; the dose of the chelators should be adjusted in the way to balance the risk of iron overload and the chelator's overload. Deferoxamine is an effective treatment for iron

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overload in thalassemia patients with cardiac problems due to its excellent effects on reducing iron overload of the heart and reducing the risk of heart failure. However, a very short half-time, the need of repetitive injections and non-targeted distribution in tissues can lead to damage to the brain, lungs, kidneys, eyes, and can cause problems such as peripheral neuropathy, glandular and growth disorders (6). Therefore, according to the high prevalence of β -thalassemia major in Iran and the importance of early detection of therapeutic-related complications, we studied and collected the most important side effects of deferoxamine to suggest a good model for the colleagues in treatment.

A wide spectrum of ophthalmic complications has been counted for deferoxamine. The most important of them are lens opacity (cataracts), optic neuropathy, changes in retinal pigment epithelium (RPE), night blindness, and visual field defects (2). Patients treated with deferoxamine may experience acute or sub-acute disturbances in visual acuity, color vision, and scotoma. Pigmented retinopathy is classically macular or peripheral. However, it may rarely be paramacular, papillomacular, or pre-papillary. Doses higher than 50 mg/kg/d increase the risk of systemic toxicity (7). Histological studies showed that deferoxamine can enlarge the RPE cells and stretches microvillus or completely perish them. Although all of the toxicities are not dose-related, high doses of deferoxamine for a long time, along with low levels of ferritin, increase the risk of the toxicity (8). According to a study conducted by Derin et al on ophthalmic complications of deferoxamine, the most common disorder was diffuse atrophy of the RPE layer with pigmented spots in the posterior polar region (macular stippling). One of the suggested mechanisms for ophthalmic toxicity of deferoxamine was the complete discharge iron, copper, and zinc from sensory retinal cells, which are important cofactors for intracellular enzymes and normal cell activity (2). Ocular toxicity may be asymptomatic; therefore, periodic ophthalmic examinations should be considered for all the patients. Monthly ferritin measurement and index therapeutic level (dose in body weight divided by ferritin level) below 0.025 reduces ophthalmic toxicity (7).

One of other counted side effects of deferoxamine is hearing problems. In a study of 1835 β -thalassemia major patients treated with deferoxamine, the prevalence of hearing loss was 27.3%, which was in both conductive and sensory-neural patterns. The amount of hearing loss is depended on the genetics and duration of deferoxamine consumption and the route of administration. Patients with more than 10 years of deferoxamine injection experience hearing loss more often. High doses of deferoxamine directly cause neurotoxicity or interfere with trace elements due to the high non-binding level of the drug depletion of trace elements induced by deferoxamine in patients with thalassemia. Like ophthalmic toxicity, doses

higher than 50 mg/kg/d increase the risk of auditory toxicity (9). However, cases of autotoxicity have been reported even at the doses below 50 mg/kg/d. A study on 100 injecting-dependent thalassemia patients, found that 3% of patients within the range of index therapy also had hearing loss. Therefore, audiometric evaluation is recommended for patients every six months. Other side effects include tinnitus and deafness, which often are reversible after ceasing deferoxamine (10, 11).

Renal complications of deferoxamine in patients with β -thalassemia major have been investigated in several studies. Patients treated with deferoxamine developed renal tubular and glomerular dysfunction and also decreased filtration rate by increased serum creatinine (12). Other renal complications were seen in β -thalassemia major include increased N-acetyl- β -glucosaminidase and decreased urinary concentration, as well as increased amino acid and protein excretion. Different mechanisms have been suggested for these side effects, the most likely of which are oxidative effects (13).

Another major side effect of deferoxamine is growth retention and skeletal changes, which are more important in children. Age under three years old and doses above 40 mg/kg/d increase the risk of developing this problem. Therefore, it is recommended that doses above 40 mg/kg/d not be prescribed until the patient's growth is complete (14).

Transfusion-dependent thalassemia patients experience immune-deficient pathologies, such as phagocytes and lymphocytes impaired functions, due to frequent transfusions and the entry of foreign antigens, as well as the possible absence of spleen. This is one of the factors that predispose these patients to infections, such as sepsis with *Yersinia enterocolitica*. This infection is common in these patients. A study in Canada on 177 beta-thalassemia major patients over 15 years found that these patients were 5000 times more likely to develop the pathogen (15, 16).

Respiratory distress has also been reported rarely in patients treated with high-dose deferoxamine. It should be noted that one of the non-dose-dependent and important side effects of deferoxamine is severe allergy, which occurs as anaphylactic shock and, in weaker states, pain and fever, which can be treated with desensitization in several stages (14).

High dose regimens, or even sometimes in standard regimens have been correlated with neurotoxicity. Several probable mechanisms for neuropathic side effects of deferoxamine have been proposed, such as multiple trace element chelation, metalloenzyme activity inhibition and oxygen based free radical generation (17, 18). Monitoring of thalassemia patients presenting with deferoxamine neurotoxicity is difficult. In patients who are asymptomatic or representing slight electrophysiological changes, decreasing the dose with serial monitoring is suggested. In symptomatic cases or cases showing electrophysiological

deterioration, temporary drug should be discontinued in lower doses with careful re-administration. In addition, deferoxamine treatment has been associated with peripheral neuropathy in thalassemia patients (19). The relevant clinical presentation includes paresthesias, myalgias and muscle weakness, although subclinical involvement detected through neurophysiologic evaluation has been reported (20).

Another important aspect of deferoxamine is contraindications. The contraindications are fungal infections, cataracts, tinnitus, sudden blindness, painful eye movement in upward-looking, severe renal failure, seizure, aluminum intoxication, lactation, and anuria (10). Deferoxamine is the standard treatment for treating patients with iron overload problems, however due to the need for frequent and long-term injections and dose-dependent toxic effects, patients should be monitored periodically for these complications. As mentioned, the risk of toxic effects in doses higher than 50 mg/kg/d is higher, hence higher doses are not recommended. Regular serum ferritin measurement and maintenance of deferoxamine therapeutic index (0.025) can prevent drug overdose and toxic effects.

Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. BK, MB and NF wrote the main body of the manuscript, MM, KA and AH significantly participated in the literature review and critically reviewed the manuscript; all the authors approved the final form of the text.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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