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Case Report

Proteinuria due to increased dose of deferasirox in a pediatric patient with thalassemia major: case report

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ABSTRACT

Deferasirox is an iron chelator that used in B-thalassemia in worldwide. Nephrotoxicity is one of the common side effects of the deferasirox. Nephrotoxicity can be seen in the form of nephritis and tubulopathy. A 6-year-old male whose ferritin levels were above 3500 ng/mL is reported in this article. Deferasirox was increased from 30 mg/kg/day to 40 mg/kg/day because of the high levels of ferritin. In complete urinalysis of the patient after 3 weeks later +3 protein was detected, and spot urine protein/creatinine ratio was 2.5. In patient without symptoms and findings, deferasirox was discontinued. In his follow-ups, no proteinuria was detected in the complete urinalysis at the second week after the drug treatment was discontinued.

Keywords: B-thalassemia, Deferasirox, Proteinuria

INTRODUCTION

Thalassemia is an inherited anemia characterized by the reduced or absent production of one or more globin chains. Beta thalassemia results in relatively high alpha globin chains due to impaired production of beta globin chains. Incompatibility between alpha and beta chains causes ineffective erythropoiesis and plays a role in the emergence of clinical findings.[1]

Iron overload due to chronic transfusions is the major problem in B-thalassemia major. The heart, liver and endocrine organs are the organs with the most iron overload.[2] The availability of chelating agents has allowed effective treatment that extend the survival, reduce side effects related to the disease by providing iron excretion. In recent years oral chelation therapy has been widely used worldwide. Optimal treatment is used for patients according to treatment compliance and drug adverse effects.[3] Deferasirox is an iron chelator used in the treatment of B-thalassemia. One of the common side effects is nephrotoxicity. It is observed approximately in 1 of 10 patients. Nephrotoxicity can be seen in the form of renal failure, glomerulonephritis, interstitial nephritis and tubulopathy.[4,5] High doses of deferasirox were found to be associated with renal tubuler epithelial cell damage in animal experiments.[6] In this article, we report a case of proteinuria developed after deferasirox dose-increase.

CASE REPORT

A male patient who has been followed up due to thalassemia major has been using deferasirox therapy for 4 years. At the control examinations of the 6-year-old patient, ferritin levels were above 3500 ng/mL. Hepatic and renal function tests were in normal limits and acute phase reactors were negative in his follow-ups. Clinical and laboratory evaluation of the patient showed no evidence of infection. As the last observed ferritin was detected as 4196 ng/ml, deferasirox was increased from

30 mg/kg/day to 40 mg/kg/day. In the tests performed before the transfusion 3 weeks later; wbc: 10770/mm^3, neutrophils 7230/mm^3, hgb: 9.8 gr/dl, plt: 347.000/mm^3, ferritin: 2388 ng/ml, AST: 45 U/L, ALT: 35 U/L, urea: 17 mg/dl, creatinin: 0.4 mg/dl. In complete urinalysis of the patient with +3 protein detected, total protein was 6.2 g/dl, albumin level was 3.2 g/dl and spot urine protein/creatinine ratio was 2.5.

In patient without symptoms and findings, deferasirox was discontinued. In his follow-ups, protein was decreased to +1 and urine protein/creatinine ratio in the complete urinalysis was decreased to 1 after one week. No proteinuria was detected in the complete urinalysis at the second week after the drug treatment was discontinued. Spot urine protein/creatinine ratio was found to be 0.3.

Table 1: Laboratory tests of the patient.

	Proteinuria and deferasirox was discontinued	1 week	2 weeks	3 weeks	6. week of 30 mg/kg/d deferasirox was started	9 weeks
Ferritin (ng/ml)	2388	-	-	2270	2560	2940
Hemoglobin (g/dl)	9.8	-	-	10.2	10.1	9.7
Urea (mg/dl)	17	-	-	25	20	23
Creatinine (mg/dl)	0.4	-	-	0.46	0.37	0.5
Urine analysis protein level	+3	+1	0	0	0	0
Spot urine protein/creatinine	2.5	1	0.32	0.31	0.36	0.36
Total protein (g/dl)	6.2	-	-	-	6	-
Albumine (g/dl)	3.2	-	-	-	3.4	-

Six weeks later, deferasirox was started at a dose of 30 mg/kg/day in patient whose control tests were normal, and proteinuria was not detected. There was no increase seen in proteinuria and spot urine protein/creatinine in control analysis. The ferritin levels of the patient were between 2000-3000 ng/ml. Proteinuria due to dose increase of deferasirox was considered. Proteinuria was not detected in the urine analysis at the 2nd week of the patient who was examined once a week after discontinuation of the drug. Spot urine protein creatinine ratio decreased to 0.32. At week 6, 30 mg/kg/day of deferasirox was restarted after no urine protein was detected. No proteinuria was observed in his follow-ups. (Table 1).

DISCUSSION

An increase in serum creatinine is the most common finding in nephrotoxicity due to deferasirox. After initiation of the medication, it is recommended to be checked once in a week and then once in a month.[7] Although deferasirox is generally well tolerated, a moderate, dose-dependent and non-progressive increase in creatinine has been observed in 36% of patients in clinical trials.[8] No increase in creatinine values due to deferasirox use was observed in our patient. In a retrospective study of 72 adult patients with thalassemia major and intermedia, treatment was terminated due to creatine elevation in 7 patients. Deferasirox-induced nephrotoxicity is thought to be more frequent in adults with accompanying diabetes.[9] Patients with B thalassemia major should be followed up with spot urine protein/creatinine ratio measured monthly for proteinuria. Proteinuria should be considered, if urine protein/creatinine ratio is ≥0.6 because urinary protein excretion is greater in beta thalassemia major compared to normal patients.[3] Aldudak et al has determined this limit as 0.7.[10]

In a study conducted in our country, proteinuria due to deferasirox was observed in 7 of 37 patients (19%). It was observed that as the deferasirox dose increased, the probability of proteinuria was increased.[11] Only one of the patients with thalassemia major who used deferasirox followed in our clinic had proteinuria. In our patient, the dose of deferasirox increased to 40 mg/kg/day and the spot urine protein/creatinine ratio increased to 2.5. High creatinine levels, low C3-C4 levels and hypoalbuminemia were not detected in laboratory tests and no clinical findings were observed on physical examination.

Dubourg et al showed that proximal proximal tubular dysfunction and a decreased GFR could be reversed by discontinuing or decreasing drug dosage.[12] In our patient, proteinuria was not detected in the urine analysis at the 2nd week of the patient after discontinuation of the drug.

CONCLUSION

Patients using deferasirox should be followed up periodically for possible nephrotoxicity in terms of renal function tests and proteinuria. Discontinuation of medication for a while or dose reduction of deferasirox may be considered when side-effects detected especially in proteinuria.

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