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HEPATOTOXICITY IN SICKLE CELL DISEASE AND THALASSEMIC PATIENTS WHO ARE TAKING EXJADE® IN BASRA

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ABSTRACT

Aim

Deferasirox is the new oral iron chelator, which is used to decrease chronic iron overload in hemoglopinopathy patient. Deferasirox can cause hepatotoxicity and induce hepatitis lead to hepatic injury and failure. This study was to estimate the frequency of hepatotoxicity in sickle cell disease (SCD) and Thalassemic patients who are taking Exjade® (deferasirox) in Basra.

Methodology

This study was conducted from April 2013 to February 2014 at Center For Hereditary Blood Diseases HBDC in Basra.The information was collected according to questioner forma include name, age, diagnosis, treatment, adverse effects included nausea, vomiting and frequency of bowel motion. The blood samples were taken from each patients and they stored at -8c for measurement of alanine aminotransferase activity (ALT), aspartate aminotransferase (AST), alkaline phosphatase activity (ALP), serum total bilirubin (TB) and serum ferritin.

Results

One hundred adult patients were 62 female: 38male. The mean of age was 25.74±10.59 years. The most of patients with age between 15-29 years (76%) and The most of patients with sickle cell disease was 60%. Among patients had nausea adverse effect (34%).There was not significant relationship between liver enzymes and TB with gender, age, the type of hemoglobinpathy and serum ferritin. There was only significant relationship between nausea scale adverse effect and ALT, AST and ALP levels.

Conclusions

The present study could not find a significant effect of any of the studied patients' characteristic with hepatic dysfunction in adult patients with sickle cell disease and thalassemia who were taking deferasirox. Therefore, hepatic dysfunction might be attributed to deferasirox use; however, it is mild in most of the cases and that reflected the accepted short-term safety of the drug.

KEYWORDS: Deferasirox, Sickle cell disease, Thalassem, Hemoglobinopathy

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INTRODUCTION

One group of blood disorders is hemoglobinopathy, which is inherited disease and resulted from abnormality either in the structure of hemoglobin like sickle cell disease or production of the hemoglobin molecule likethalassemia syndrome [1,2] leading to an ineffective erythropoiesis (the production of red blood cells).[3]

The prevalence of carriers of any type of hemoglobin gene variant is lowest in European region 3.3% of population and is highest in South-east Asian region 45.5%, African region 44.4% and Eastern Mediterranean region 21.7%.[4] Although the world wide prevalence of hemoglobin disorders is variable but both thalassemia and sickle cell anemia are widely spread throughout Arab Peninsula from south to Iraq in north and Mediterranean region.[5] Basra, south of Iraq, is endemic area for both sickle cell disease (14.8%) and thalassemia (5%).[6,7]

Iron overload in hemoglobinopathies could be due to increase absorption of iron, blood transfusion and chronic hemolysis.[8] Iron chelation therapy is necessary used to prevent organ damage and decrease mortality because chronic iron overload could lead to multiorgan dysfunction and/or failure like liver, heart and endocrine.[9]

Deferasirox is the new oral iron chelator, which is used to decrease chronic iron overload in hemoglopinopathy patient.[10] The main adverse effects appeared with the use of deferasirox are a mild to moderate increase of the creatinine and liver enzyme levels.[11] Other severe adverse effects include Fanconi syndrome, cytopenias, irreversible renal and liver failure.[12,13]

Deferasirox can cause hepatotoxicity and induce hepatitis lead to hepatic injury and failure.[13,14] Deferasirox induce liver injury by several mechanisms including cytochrome P450 production reactive intermediates which are covalent bonding with necessary cellular components like nucleic acids and proteins lead to cellular dysfunction, [15,16] stimulation of autoimmunity, disruption of calcium homeostasis, canalicular and mitochondrial injuries, macrovesicular lesions, fibrosis and cholestasis.[15,17]

The aim of this study was to estimate the frequency of hepatotoxicity in SCD and thalassemicpatients who are taking deferasirox in Basra.

MATERIAL AND METHODS

The study was conducted from April 2013 to February 2014 at Center For Hereditary Blood Diseases HBDC in Basra.[INT4]Sixty patients with sickle cell disease and fourty patients with thalassemia, the included patient were adult age >15 years who were taking deferasirox (20-40 mg/kg) through different duration of treatment. The excluded patients who were taking hydroxyurea, as well as those who had viral hepatitis.

The information was collected according to questioner forma include name, age, diagnosis, treatment, adverse effects included nausea, vomiting and frequency of bowel motion.[18]

The blood samples were taken from each patients and they stored at -8c for measurement of ALT and AST by Randox kit depended on colorimetric method (Reitman and Frankel, 1957),[19] alkaline phosphatase activity (ALP) by Biolabo kit depend on optimized method based on SCE (Scandinavian Society of Clinical Chemistry) and DGKC (German Society of Clinical Chemistry, 1972),[20] serum total bilirubin (TB) by Biolabok it depend on colorimetric method **(**Malloy-Evelyn modified by Walters) [21] and serum ferritin by Elabscience depend on colorimetric method .[22]

Statistical Analysis

The data of this study was analysis by SPSS version 15. Where the t-test used to find the relationship between the parameters (ALT, AST, ALP and TB) with gender and diagnosis. Also the correlation coefficient used for find the relation between the levels of ALT, AST, ALP and TB with the level of serum ferritin. NOVA was used to find therelationship between parameters (ALT, AST, ALP and TB) with age, nausea, vomiting and bowel motion frequency scales.

RESULTS

One hundred adult patients were 62 female:38male. The mean of age was 25.74±10.59 years. The most of patients with age between 15-29 years (76%) and The most of patients with sickle cell disease was 60%. Among patients had nausea adverse effect (34%) as shown in table 1.

The frequency of ALT was 9% (10% with SCD and 7.5% with thalassemia), AST was 23% (20% with SCD and 27.5% with thalassemia), ALP was 33 % (23.3% with SCD and 47.5 % with thalassemia) and TB was 59% (50% with SCD and 72.5% with thalassemia) as appeared in table 2.

There was not significant relationship between liver enzymes and TB with age, gender and the type of hemoglobinopathy as shown in table 3 and the correlation between parameters (ALT, AST, ALP and TB) and serum ferritin was not significant as shown in table 4.

There was significant relationship between nausea scale and ALT, AST and ALP. On other hand the relationship between vomiting scale and frequency of bowel motion and ALT, AST, ALP wasn't significant. The relationship between TB and all adverse effect was not significant as appeared in table5.

Table 1: General Characteristics of Hemoglobinopatheis Patients

Characteristics of Patients	Total Patients
Male	38
Female	62
Mean of ages (years)	25.74±10.59
15-29 years	76 (76%)
30-44 years	16 (16%)
45-60 years	8 (8%)
Types of hemoglobinopatheis	
Thalassemias	40 (13 male &27 female)
Sickle cell disease	60 (25 male &35 female)
Total	100
Patients rating of adverse effects	
Nausea	34 (34%)
Vomiting	11 (11%)
Frequency of bowel motion	10 (10%)

Table 2: The Frequency of Elevated of ALT, AST, ALP and TB According to Diagnosis

Parameters	Sickle Cell Disease (60 Patients)	Thalassemias (40 Patients)	Total Number of Hemoglobunopathy Patients (100 Patients)
	The Percent of Patients with Elevated Levels of Parameters		
ALT	10%	7.5%	9%
AST	20%	27.5%	23%

Table 2: Contd.,			
ALP	23.3%	47.5%	33%
TB	50%	72.5%	59%

Table 3: The Relationship between Parameters (ALT, AST, ALP and TB) with age, Gender and Diagnosis of Patients

Age, Gender and Diagnosis of Patients	Parameters			
	ALT	AST	ALP	TB
Age of patients 15-29 years Mean±Std	16±16.744 U/L N=73	27.438±24.985 U/L N=73	21.671±27.914 IU/L N=70	43.522±29.364 mg/dL N=71
30-44 years Mean±Std	16.533±16.544 U/L N=15	22.333±21.090 U/L N=15	23.815±31.108 IU/L N=13	41.053±31.224 mg/dL N=15
45-60 years Mean±Std	11.250±8.988 N=8	17.125±13.239 N=8	13.714±2.690 N=7	36±24.399 N=7
P value	P< 0.719	P< 0.423	P< 0.721	P< 0.793
Gender of patients Male Mean±Std	15.486±16.326 U/L N=37	27.222±23.411 U/L N=36	18.531±21.471 IU/L N=35	46.650±31.558 mg/dL N=34
Female Mean±Std	15.867±16.035 U/L N=60	25±23.841 U/L N=61	22.982±30.116 IU/L N=56	39.897±27.477 mg/dL N=60
t-test P value	0.113 < 0.911	0.446 < 0.656	0.761 < 0.449	1.085 < 0.281
Diagnosis Thalassemia Mean±Std	16±15.528 U/L N=38	26.461±23.176 U/L N=39	19.974±28.589 IU/L N=38	38.868±27.333 mg/dL N=38
Sickle cell disease Mean±Std	15.542±16.527 U/L N=59	25.396±24.047 U/L N=58	22.2±26.177 IU/L N=53	44.695±30.147 mg/dL N=56
t-test P value	0.136 < 0.892	0.217 < 0.829	0.385 < 0.701	0.954 < 0.342

Table 4: The Correlation between Parameters (ALT, AST, ALP and TB) and Serum Ferritin

Parameters	Serum Ferritin Levels	
	Correlation Coefficient (r)	Significant
ALT	r = 0.138	P < 0.1
AST	r = 0.135	P < 0.106
ALP	r = -0.076	P < 0.248
TB	r = -0.092	P < 0.201

Table 5: The Relationship between Parameters (ALT, AST, ALP and TB) and Nausea , Vomiting and Bowel Motion Frequency Scales

Parameters	Nausea Scales	Vomiting Scales	Frequency of Bowel Motion
ALT	F = 8.202 P < 0.0001	F = 0.394 P < 0.757	F = 0.769 P < 0.467
AST	F = 2.699 P < 0.05	F = 0.77 P < 0.514	F = 0.411 P < 0.664
ALP	F = 6.557 P < 0.0001	F = 0.152 P < 0.928	F = 0.09 P < 0.914
TB	F = 1.173 P < 0.324	F = 1.087 P < 0.359	F = 0.06 P < 0.942

DISCUSSIONS

Deferasirox can induce hepatic toxicity and hepatic injury in hemoglobinopathy patients,[14] which can be indicated

by elevated of serum ALT, AST, ALP enzymes and TB levels.[23]

In this study,ALT was increased in 9% of ptients, AST was elevated in 23% of patients, and ALP level was elevated in one third of patients (33%) and this result was nearly from Vichinsky et al study and Eshghi P et al study (5.6 and 5.89%),[24,25] while the other studies appeared different results like Mevada et al study and Reddy et al study (44.8 and 45.83%). [26,27] Also the same studies revealed that deferasirox could affect liver activity resulting in elevation of liver enzymes levels. [(24-27)] Although there was no significant relation between the type of hemoglobinopathy in this study and the level of liver enzymes which might support the issue of deferasirox induced hepatotoxicity. But other studies could find some effect of disease itself. In sickle cell disease e.g. hepatic dysfunction caused by intrahepatic sickling process of erythrocytes,[28] acute ischemia with vascular occlusion, cholestasis and hepatic sequestration crisis.[29] On the other hand, chronic iron overload in patients with hemoglobinopathies that was due to an increased iron absorption and lack of an effective mechanism for excretion could lead to accumulation of iron and deposition into multiple organs including liver causing hepatic dysfunction.[9]

In this sudy, the liver enzyme levels were more elevated in thalassemic patients than in sickle patients because SCD might be have protective effect from iron-related organ dysfunction and the patients have less risk for organ injury than thalassemic patients[30] and sickle patients had higher levels of γ-tocopherol (antioxidant) than thalassemic patients. γ-tocopherol may play an important role in reducing tissue injury related to oxidant stress and inflammation.[31]

The TB levels was highly elevated in 59% of patients, which is one of the parameters that indicate hepatic dysfunction.[23] This elevation could be due to deferasirox treatment,[32] hemolytic state, or hepatobiliary causes, extrahepatic obstruction or hepatic sequestration.[33]

In the present study, there was no significant relationship between liver enzymes and TB with the gender and the age of patients. This result agreed by Kotila et al and Emokpae et al studies, they found the elevation of liver function tests was not related to gender and age in hemoglobinopathy patients, so the appreciable elevation in liver enzymes might be due to complications arising from treatment of the disease or disease itself. [34,35]

The relationship between liver enzyme levels and TB with serum ferritin was not significant. Asif M et al (2014) found a weak insignificant correlation between serum ferritin and liver enzyme levels in thalassemic patients; they attributed that to direct toxic effect of iron on hepatocytes.[36] Smith E et al suggested that both serum ferritin and liver iron content correlated with liver injury but using ferritin alone was not significantly correlated with ALT.[37]

In this study the relationship between nausea scale and ALT, AST and ALP levels was significant and this relation could be explained by the hepatic inflammation and injury associated with abdominal pain and nausea.[38] On other hand, the other adverse effects like vomitingand frequency of bowel motion had insignificant relation with the same parameters. That might be due to that some of studied patients were taking antiemetic and ant diarrheal medicines during deferasirox treatment period. Other studies suggested hepatic impairment and the elevation of liver function test associated with symptoms include vomiting and diarrhea.[38,39]

CONCLUSIONS

In conclusion, the present study could not find a significant effect of any of the studied patients' characteristic with hepatic dysfunction in adult patients with sickle cell disease and thalassemia who were taking deferasirox. Therefore, hepatic dysfunction might be attributed to deferasirox use; however, it is mild in most of the cases and that reflected the

accepted short-term safety of the drug. Further studies that are more comprehensive are required to evaluate the overall safety and efficacy and to study the dose related toxicity.

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