Changes of some Liver Function Tests with Regular and Irregular Desferroxamine Therapy in β-Thalassemic Patients

Dr. Mohammad A. Al-Kataan * Shaimaa D. Al-Shakarchi*

ABSTRACT

Background and Objectives: (a) To determine the effect of regular desferroxamine (DFO) therapy on De-Ritis ratio. (b) To determine the changes in some liver function test parameters between patient on regular DFO and those with irregular DFO therapy.(c)To determine the relation between serum iron and serum ferritin in both groups. (d) To determine the effects of age, sex and body mass index (BMI) on measured parameters in both groups.

Methods: This study was conducted at Thalassemia Center /Ibn-Al-atheer Pediatric-Hospital in Mosul from October 2007 to April 2008. Forty patients with β- Thalassemia were selected as follow: twenty patients with regular DFO therapy and other twenty with irregular DFO therapy.

Results: De-Ritis ratio serum Ferritin, Ferritin: total serum protein ratio and total serum protein shows no significant changes between both groups. Serum ALT, AST, ALP activities and serum iron shows significant increase in those with irregular DFO therapy ($P< 0.01$).

Conclusions: Irregular DFO therapy shows significant effects on serum iron and some other liver function test parameters that indicate chronic hepatocytes damage without

INTRODUCTION:

A known consequence of regular blood transfusion in patients with β- thalassemia (BT) major is iron overload which is associated with injury to heart, liver and endocrine organs. Chelation therapy with desferroxamine (DFO) for iron overload has been used to reduce toxicity.[1] A high dose of DFO treatment, however may be complicated by neurotoxicity [2], skeletal muscle dysplasia and growth retardation.[3, 4, 5] The degree of iron overload is therefore important for the adjustment of chelating dose; because the liver is the largest iron-store. Liver iron concentration has been taken to represent total body iron store. [5] Hepatocytes damage that occur due to secondary iron overload arises from the sustained condition of oxidative stress,[6] Although hepatic iron excess is characterized by a low degree of and hepatocellular necrosis, this low necrogenic activity may initiate and promote progressive fibroclerosis, eventually cirrhosis. [6] Elevated serum activities of ALT and AST was observed in thalassemic patients with iron overload.[7] Regular dose of DFO reduces liver enzymes progressively and it may reach near to normal values.[8] Many studies have correlated serum ferritin to serum iron and ALT activity in thalassemic patients and have use it as an index for sufficient DFO dosing.[7] This study aimed to fill the gab in the knowledge that concerning with the effects of regular and irregular DFO regimen on hepatocellular injury in thalassemic pateint with transfusional iron overload.

PATIENTS METHODS:

This study was conducted at Thalassemia Center/ Ibn-Al-Atheer Pediatric-Hospital in

*College of Pharmacy/ Dep. Clinical Pharmacy / College of Pharmacy, Mosul University

Forty patients with β-Thalassemia major were selected as follow: twenty patients on regular DFO therapy and twenty on irregular DFO therapy. Both groups were under single blood transfusion/month with DFO dose of 40-60mg/kg/day for 5-6 days/ week, the first group follow up their recommended dose of DFO while the second group was not . Serum iron was measured by Ferrozine method,[9] Serum Ferritin was assayed by Turbidimetery-Latex method,[10] ALT and AST activity were measured by Wootton and Freeman method,[11] ALP activity was measured by Kind and King method,[12]. Total serum protein was assayed by Biuret method.[13] De-Ritis ratio which is considered as an index of acute liver injury[13] and Ferritin: Total Serum proteins were calculated by equation as follow [13] :

De-Ritis ratio = ALT / AST activity.

Fer./ TSP= Ferritin/ total serum protein

Data were represented as mean ± SD, 2-sample t-test and the effects of age, sex and BMI were obtained by Pearson-Correlation.

RESULT:

De-Ritis ratio, serum Ferritin, Ferritin/TSP ratio and total serum protein shows no significant changes between both groups. Serum AST,ALT and ALP activities and serum iron show significant increase in patients with irregular DFO therapy ($P< 0.01$). Serum iron was significantly correlated to Serum ALT activity and Serum Ferritin ($P < 0.01$) in patients with irregular DFO therapy. BMI correlated to ALP activity ($P < 0.05$) in those with irregular DFO therapy, while age and sex shows no significant correlation to any of the measured parameters in this group of patients. In patients with regular DFO therapy serum iron correlated to Serum AST and ALP activity ($P < 0.05$).Age was significant correlate to Serum Ferritin ($P < 0.01$), sex and BMI show no significant correlation to any of the measured parameters.

Table 1: De-Ritis ratio and Some Other Liver Function Test Parameters in Patients with Regular and Irregular DFO Therapy

	Parameters	Regular DFO therapy	Irregular DFO therapy
1	Serum Iron µg/dl	130.3 ± 15.2	188.2 ± 10.8***
2	Serum Ferritin µg/dl	1822 ± 270	1913 ± 273
3	De-Ritis Ratio	1.395 ± 0.167	1.420 ± 0.134
4	ALT-activity IU/L	52 ± 7.9	71 ± 11.3***
5	AST-activity IU/L	37.58 ± 6.83	49.94 ± 7.28***
6	ALP-activity IU/L	83.53 ± 8.21	119.7 ± 16.5***
7	Ferritin:TSP	2.34 ± 0.37 × 10-4	2.46 ± 0.33 × 10-4
8	TSP g/L	76.26 ± 4.31	75.95 ± 3.46

P< 0.05= *, P<0.01= **, P< 0.001=*

DISCUSSION:

In the present study, De-Ritis ratio which was used as an indicator for acute hepatocellular damage show no significant change in patients with irregular and regular DFO therapy and this can be explained by the fact that all patients present with chronic low grade inflammatory process that occur due to increase oxidative stress in the hepatocytes [6] and leading to cell membrane damage that is reflect as an increase in serum ALT and AST activities which end by fibrogensis [14] and leading to non significant increase in De-Ritis ratio because both enzymes will increase in the same manner. Fibrogensis process leads to significant increase in the serum ALP activity in those with irregular DFO therapy, due to positive iron balance and failure of Chelation therapy to stop Fonton reaction. [15] .The hepatocellular damage in thalassemic patient with irregular DFO therapy was assessed by aminotransfarases activities and serum Ferritin level. Irregular DFO patients show significant increase in serum activities of liver enzymes this can be explained by the fact that liver enzyme leak from the cytoplasmic and mitochondrial compartments of injured hepatocytes to plasma[16]. Serum Ferritin decreases in non-significantly in patients with regular DFO therapy and this is due to regular DFO therapy will induce negative iron balance and so reduce iron body store[17] . Serum Ferritin/TSP ratio shows non significant increase in those with irregular DFO therapy and this may be due to irregularity of DFO therapy[15]. When serum iron is increased it result increase rate of Fonton reaction that associated with increase in the oxidative stress that aggravate the inflammatory process in this group of patients[15].

CONCLUSION:

Irregular DFO therapy lead to significant increase in serum iron and some liver used as an indicator for acute hepatocytes damage.

RECOMMENDATION:

1-Patient should be educated and follow up for taking their DFO therapy and how to use their DFO pump.

2-Patient should be submitted to regular check for their iron status that include serum iron, serum Ferritin , serum transferrin and saturation %.

REFERECNES:

1. Olivieri NF, Brittenham GM. Iron chelation therapy and the treatment of thalassemia. Blood . 1997; 89: 739-761.
2. Olivieri NF, Buncic JR, Chew E et al. Visual and auditory neurotoxicity in patients receiving subcutaneous desferroxamine infusion. N.Engl.J.Med 1986; 314:869-873.
3. Hartkamp M, Babyn P., Olivieri NF. Spinal deformities in desferroxamine treatment homozygns β- thalassemia major patients. Pediatr Radiol 1993; 23:525-528.
4. De-Sancitis V., Pinamonti A., Di Palma et al. Growth and development in thalassemia major patients with bone lesion due to desferroxamine. Eur J Pediatr .1996; 155:368-372.
5. Chan Y., Li C., Pang L. et al. Desferroxamine-induced long bone changes in thalassemic patient-radiographic features, prevalence and relation with growth. Clin Rad. 2000; 55:610-614.
6. Poli G. Pathogenesis of liver fibrosis; role of oxidative stress. Mol Aspects Med. 2000; 2:49-98.
7. Jensen P., Jensen F., Christensen T. et al. Relationship between hepatocellular injury and transfusional iron overload prior and during iron chelation with desferroxamine: a study in adult patients with acquired anemia. Blood . 2003; 101; 1:91-96.
8. Chan Y., Li C., Law M. et al. Liver volume in thalassemia major: relationship with body weight, serum ferritin and liver function test. Pediatr Radiol 2005; 35:165-168.
9. Stookey L. Ferrozine. A new spectrophotometric reagent for iron. Anal Chem .1970; 42:779-781.
10. Bemard A., Lanwerys R. Turbidimetery-Latex immunoassay for serum ferritin.J Immunol Methods. 1984; 71:141-147.
11. Wootton I., Freeman H..Microanalysis in medical biochemistry. 6 th ed. Curchill Livingstone, Edinburgh, England . 1982; 102-105.
12. Kind R., King E. Estimation of plasma phosphatase by determination of hydrolysed phenol with aminoantipyrine. J. Clin Path. 1954; 7:322-326.
13. Buritis C., Ashwood E. Tietz textbook of clinical chemistry. 3 rd ed. Saunders Company, USA.

14.Prati D., Taioli E., Zanella A. et al. Updated definition of healthy ranges for serum alavin-aminotransfarase levels. Ann Intern Med. 2002; 137:1-10.
15.Arora A., Goros G. The role of metals in ischemia/ reperfusion injury of liver. Semin Liver Dis. 1996; 16:31-38.
16.Boyd W.. The Intracellular distribution, latency and electrophortic mobility of L-glutamic oxaloacetic transaminase. Biochem J .1970; 8:433-438.
17.Inoue M., Protective mechanism against reactive oxygen species in : Arias M, Bojer L., Fansto N. et al. The liver biology and pathology. Raven Press, New York, USA. 1994; 443-459.