IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 6 Ver. VIII (June. 2017), PP 68-72
www.iosrjournals.org

Observation of Liver Function Test In Patient of Pulmonary Tuberculosis Taking DOTS Regimen

*Dr. Pradeep Prasad[1],Dr. Mukesh Kumar Niraj[2]
[1]*Senior Resident, Department of Laboratory Medicine, Rajendra Institute of Medical Sciences, Ranchi.*
[2]*Tutor, Department of Biochemistry, MGM College & Hospital, Jamshedpur.*
Corresponding author: Dr. Pradeep Prasad1

Abstract:
Introduction: *Tuberculosis is one of the most ancient diseases known to mankind which was traced and documented from ancient ayurvedic system practiced by sushrutha, charak and other around 2500 BC. There is wide variation in the reported incidence of Anti-tubercular drug induced hepatotoxicity by different workers and there is paucity of work with anti-tubercular drug induced hepatotoxicity under DOTS regimen in the part of this country.*
Material and Method: *A total of 75 patients of pulmonary tuberculosis entered the study. Patients who were not followed properly were dropped from this study. This eliminated 15 cases initially enrolled so that 60 were available for analysis.*
Results: *After treatment most of the patients developed elevated liver enzymes from its pre-treatment level but the enzyme levels declined with treatment continued. One patient had mild elevation of transaminases level and does not developed symptoms of hepatic toxicity and treatment continued without interruption.*
Conclusion: *Anti-tubercular drugs given under DOTS regimen resulted in less incidence of hepatic dysfunction. In majority of cases the elevation of serum enzymes was self limiting which came down in spite of continuing therapy. The elevation of enzymes was seen mostly after four weeks of treatment. The increase activity of liver enzymes was higher in patient above 35 years of age.*
Keywords: *Anti-tubercular drugs, DOTS regimen, Tuberculosis and hepatotoxicity.*

I. Introduction

Tuberculosis is one of the most ancient diseases known to mankind which was traced and documented from ancient ayurvedic system practiced by sushrutha, charak and other around 2500 BC. It has also been documented in the Vedas and Ayurvedic samhitas as early as 2000 BC. The land mark discovery of causative agent of tuberculosis by Sir Robert Koch was announced on 24th March 1882[1]. Tuberculosis remains a world wide public health problem. Based on suveillance and survey data, It is estimated that there were 8.9 million new cases of tuberculosis in 2004 (140 per 100000 population) including 3.9 million (62 per 100000 population) new smear positive cases of which 0.47 million adults were HIV positive[2]. There were 14.6 million (95 per 100000 populations) where smear positive. It is estimated that 1.7 million people (27 per 100000 populations) died from tuberculosis in year 2004 which include 0.248 million cases co-infected with HIV. So there is re-emergence of tuberculosis infection due to the HIV[2]. Tuberculosis kills more adult than any other infectious disease. Eight out of Ten of all those struck by Tuberculosis are economically productive age group of 15-49 years. India is the highest tuberculosis burden country in the world and accounts for nearly one fifth (20%) of global burden of tuberculosis. Every year approximately 1.8 million person developed tuberculosis of which about 0.8 million are new smear positive highly infectious case. 2 of every 5 Indians are infected with tuberculosis bacillus. Every day about 5,000 people more than 1000 people die every day and almost 0.4 million die every year[3].

Today's India's DOTS programme against tuberculosis is recognized as the fastest expanding programme. The government of India, WHO and World Bank together reviewed the National Tuberculosis Programme in year 1992, and recommended the revised strategy known as Revised National Tuberculosis Control programme (RNTCP) which incorporates the strategy called DOTS (Directly Observed Treatment, short course chemotherapy). It was launched full fledge in March 1997 and has covered whole country by March 2006[4].A higher dose antitubercular drug has been shown to be associated with drug induced hepatotoxicity. The risk of drug induced hepatotoxicity with isoniazid rifampicin combination has been shown to be lower with intermittent than daily therapy. Under DOTS programme a thrice weekly intake of antitubercular drugs, the efficacy as well as the drug tolerance has been encouraging. The routine monitoring of the serum bilirubin, ALT, AST, and Alkaline phosphatase has been advocated to get early detection of adverse reaction of the anti-tubercular drugs. By screening of these liver function tests the development of sever hepatic damage from these drugs can be prevented and warned timely to rapidly developing drug induced hepatitis.

There is wide variation in the reported incidence of Anti-tubercular drug induced hepatotoxicity by different workers and there is paucity of work with anti-tubercular drug induced hepatotoxicity under DOTS regimen in the part of this country. So the present study is being undertaken to observe the effect of Anti-tubercular drugs on the liver function test in the patients of pulmonary tuberculosis in the initial phase of treatment under the DOTS chemotherapy regimen.

II. Materials And Methodology

The present study has been carried out in patients of pulmonary tuberculosis who were admitted in the Indoor department, TB and Chest unit, DOTS centre and also from outpatient department of Rajendra Institute of Medical Sciences, Ranchi. A total of 75 patients of pulmonary tuberculosis entered the study. Patients who were not followed properly were dropped from this study. This eliminated 15 cases initially enrolled so that 60 were available for analysis. For study according to DOTS regimen Anti-tuberculosis drugs are given to all patients. At the time of admission routine blood tests were done for base line study. Those with derangement of any Liver Function tests were not included in the present study. Particular attentions were paid to the presence of liver enlargement or jaundice to those admitted patients. At the time of selection of cases, patients of pre-existing liver disease, Heart disease, Hematological disorder, Diabetes, Alcohol abuse, Hepatotoxic drug, recent history of amenorrhea (in case of female patients having chance of pregnancy) and having history of recent blood transfusion, and patients in extrapulmonary tuberculosis were excluded from and study. Serial estimation of serum Bilirubin, serum ALT, serum AST, serum Alkaline phosphatase were done in the patients of study group. First of these were done at the time of admission, and then serial successive estimation was done after the four weeks of treatment and after the eight weeks of treatment.

III. Results

Statistical Analysis: The data was analyzed by using SPSS 20 software. The data is presented in percentages, rates and ratios. Chi square test was used to find the association between attributes.

Table – I: Showing Bilirubin (mg/dl), ALT (U/L), AST (U/L) and Alkaline Phosphatase (U/L) at the time admission in total numbers of observations.

Sl.No.	Tests	Range	Mean	S.D.	S.E.
1.	Sr. Bilirubin	0.6 - 0.9	0.68	0.09	0.01
2.	Sr. ALT	12 - 21	15.47	2.10	0.02
3.	Sr. AST	14 - 22	17.12	2.24	0.29
4.	Sr.Alk.Phos.	147-162	156.72	2.90	0.37

Table – II: Showing Bilirubin level (mg/dl) after four weeks of treatment Sex wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	Male	30	0.6 - 1.0	0.76	0.10	0.018
2.	Female	30	0.6 - 4.1	0.97	0.79	0.14

Table – III: Showing Bilirubin level (mg/dl) after four weeks of treatment Age wise distribution

Sl.No.	Sex	No. Of Observation	Range	Mean	S.D.	S.E.
1.	15 - 30	26	0.6 - 1.0	0.79	0.10	0.02
2.	31- 50	26	0.6 - 4.1	0.98	0.85	0.16
3.	Above 50	08	0.6 - 0.8	0.72	0.07	0.02

Table – IV: Showing ALT level (U/L) after four weeks of treatment Sex wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	Male	30	15 – 92	25.70	15.55	2.83
2.	Female	30	14-212	32.17	44.01	8.03

Table – V: Showing ALT level (U/L) after four weeks of treatment Age wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	15 - 30	26	15 – 92	25.15	16.25	3.18
2.	31- 50	26	14 – 212	34.58	46.85	9.19
3.	Above 50	08	16 – 42	24.12	10.46	3.70

Table – VI: Showing AST level (U/L) after four weeks of treatment Sex wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	Male	30	17 – 101	29.37	16.82	3.07
2.	Female	30	17 – 218	35.60	45.16	8.24

Table – VII: Showing AST level (U/L) after four weeks of treatment Age wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	15 - 30	26	17 – 101	28.19	17.87	3.50
2.	31- 50	26	17 – 218	37.85	47.98	9.41
3.	Above 50	08	18 – 47	29.00	12.31	4.35

Table – VIII: Showing Alkaline phosphatise level (U/L) after four weeks of treatment Sex wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	Male	30	174-317	202.00	38.84	7.09
2.	Female	30	174-443	212.57	69.04	12.60

Table – IX: Showing Alkaline Phosphatase level (U/L) after four weeks of treatment Age wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	15 - 30	26	174-317	206.27	43.22	8.47
2.	31- 50	26	174-443	210.38	69.77	13.68
3.	Above 50	08	186-279	213.25	39.05	17.81

Table – X: Showing Bilirubin level (mg/dl) after eight weeks of treatment Sex wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	Male	30	0.6 - 1.0	0.75	0.08	0.01
2.	Female	30	0.6 - 3.8	0.93	0.72	0.13

Table – XI: Showing Bilirubin level (mg/dl) after eight weeks of treatment Age wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	15 - 30	26	0.6 -1.0	0.76	0.92	0.01
2.	31- 50	26	0.6 -3.8	0.96	0.78	0.15
3.	Above 50	08	0.6 -0.8	0.72	0.07	0.02

Table – XII: Showing ALT level (U/L) after eight weeks of treatment Sex wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	Male	30	16 - 71	23.87	11.35	2.07
2.	Female	30	14 -170	30.00	37.53	6.85

Table – XIII: Showing ALT level (U/L) after eight weeks of treatment Age wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	15 - 30	26	16 - 71	23.27	12.15	2.38
2.	31- 50	26	14 - 17	32.08	39.88	7.82
3.	Above 50	08	16 - 38	22.12	8.25	2.91

Table – XIV: Showing AST level (U/L) after eight weeks of treatment Sex wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	Male	30	18 - 85	27.40	13.32	2.43
2.	Female	30	18 - 175	33.40	38.86	7.09

Table – XV: Showing AST level (U/L) after eight weeks of treatment Age wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	15 - 30	26	18 - 85	27.04	14.25	2.79
2.	31- 50	26	18 - 175	35.00	41.39	8.11
3.	Above 50	08	18 - 42	26.38	3.39	3.32

Table – XVI: Showing Alkaline Phosphatase level (U/L) after eight weeks of treatment Sex wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	Male	30	164-283	194.00	35.41	6.46
2.	Female	30	164-390	197.33	55.48	10.13

Table – XVII: Showing Alkaline Phosphatase level (U/L) after eight weeks of treatment Age wise distribution

Sl.No.	Sex	No. of Observation	Range	Mean	S.D.	S.E.
1.	15 – 30	26	164-283	193.62	38.23	7.49
2.	31- 50	26	164-390	196.15	56.28	11.03
3.	Above 50	08	176-253	202.00	36.47	12.89

IV. Discussion

This work is concerned with the estimation of Sr.Bilirubin, ALT, AST and Alkaline phosphatase during the treatment with anti-tubercular drugs in the patients of pulmonary tuberculosis taking DOTS regimen. isoniazid, rifampicin, ethambutol, and pyrazinamide have been successful therapeutic agents for the treatment of TB because of their high therapeutic efficacy and good patient acceptance. However, a variety adverse reaction to these drugs has been reported. Liver toxicity is the most common adverse effect. **Liver Function Tests at the time of admission:** At the time of admission level of Sr. Bilirubin, ALT, AST, and Alkaline phosphatase shown in table, 2, as serum bilirubin ranges from 0.6 to 0.9mg/dl, mean 0.68, SD 0.09, and SE 0.0.1. serum ALT ranges from 12 to 21U/L, mean 15.47, SD 2.10 SE 0.20 serum AST ranges from 14 to 21U/L, mean 17.12, SD 2.24, SE 0.29 serum Alkaline phosphatase ranges from 147 to 162, mean 156.72, SD 2.90, SE 0.37.Value of serum bilirubin, ALT, AST, and Alkaline phosphatase depends upon the method applied. In present study, estimation was done with auto analyser AU480. According to these methods the normal value of serum bilirubin range from 0.3 to 1.3 mg/dl, serum ALT 0 to 40 U/L, serum AST 0 to 38U/L and serum Alkaline phosphatase 80 to 290 U/L. So the findings at the time of admission are within the normal range.

Liver function tests after treatment: After treatment most of the patients developed elevated liver enzymes from its pre-treatment level but the enzyme levels declined with treatment continued. One patient had mild elevation of transaminases level and does not developed symptoms of hepatic toxicity and treatment continued without interruption. Two patients developed significant elevation of liver enzymes (3.3%). In the present study 3.3% of patients developed hepatotoxicity, which is matches figures reported in previous studied on DOTS regimen in Bangladesh by Begum Iutfun Nahar et. Al[6]. (2006), Dhingra VK et. al.(2004), S.K. Sharma et. Al[5]. (2006). Wide variations have been found in the reported incidences of hepatotixicity during anti-tubercular therapy. Zierski M, Bek E. (1980) reported hepatotoxicty with anti-TB drugs with short course chemoptherapy was 9%. Hong Kong study (1981) reported 2% of patients develop hepatitis. ParthaSrthy R. et. al. (1986) reported 2-8% hepatotoxicity in pulmonary tuberculosis patients. N.P. Thompson et. al. (1995) study done in UK shows abnormalities in liver function tests in 10-25% of patient, Clinical hepatitis developed in about 3% of cases. De souza AF etal. (1996) reported 6% clinical and lab. Sign of liver cell injury, study conducted in Brazil. Tuktas H. et. al.(1994) observation done in Taipei in which an incidence of 14.7% of anti-TB drug induced hepatotoxicity was reported. Vidal pla R. (1991) reported 16.5% incidence of hepatotoxicity with 3.5% of sever form. Yoshiyama T.et. al. (1999) study with short course chemotherapy in Japan found incidence of hepatotoxicity was 8%. Ohno M.et. al[8]. (2000) in Japan indicated an incidence rate 18.25% of hepatotoxicity. Wada M. (2001) reported an incidence rate of 7.9% of anti. TB drug induced hepatotoxicity. Huang YS et. Al[9]. (2002) study performed in Hong Kong showed an incidence of 14% in Chinese patients. Rajani Shakya et. Al[10] .(2004) study performed in Nepal reported 8% incidence of hepatotoxicity. Gulbay BE et. al. (2006) reported 2.4% incidence of hepatotoxicity and there no age or gender difference were observed. Kwok chin chang (2006) studied on standard anti-TB and hepatotoxicity, he found that thrice weekly regimen had low incidence of hepatotoxicity (4.1%). Khalid Mahmood et.al[7]. (2007) study conducted in Pakistan reported incidence of hepatotoxicity was 19.76%. Chang KC (2008) reported 5% incidence of hepatotoxicity was considered when serum alanine transaminase exceeds three times the upper limit of normal.

The adverse drug reactions are however lesser with intermittent drug regimen as in DOTS under RNTCP. A study conducted at New Delhi Tuberculosis centre the incidence of hepatotoxicity during DOTS therapy was observed only 1% by Dhingra VK et. al. (2004). S.K. Sharma, P.K. Sinha[5] (2006) study performed in AIIMS New Delhi DOTS centre show elevated serum aminotrasnferases in 3% of cases but patients did not have symptoms and laboratory abnormality of sever hepatotoxicity. Begum lutfun nahar et. Al[6]. (2006) study performed in Bangladesh under DOTS, she observed that 2.94% of patients developed drug induced hepatotoxicity. In present study which based on DOTS developed incidence of hepatotoxicity was 3.3%, which is slightly higher than the previous studies.

The time interval from initiation of treatment to the onset of heptotoxicity was initial four to five weeks. It may be earlier before four weeks because of lack patient's awareness about hepatotoxic effects and laboratory delay of reports exact duration was lacking but most of patients have elevated liver enzymes within the four to five weeks. Dhingra et. al. (2004) reported that most of the adverse reactions observe within first four weeks of treatment. Begum lutfun nahar et. Al[6]. (2006) reported hepatotoxic effects are occurs during initial phase of treatment. Ohno M. et. Al[8]. (2000) study done in Japan reported adverse hepatic reaction in first month of isoniazid and refampicin treatment. Shakya et. al. (2004) study conducted in Nepal reported time interval for onset of hepatotoxicity after initiation of therapy was 12 to 60 days (median 28 days). Khalid Mahmood et. Al[7]. (2007) reported that most of the patients develop hepatotoxicity within two weeks of starting of therapy. Kwok Chin Chang (2006) reported hepatotoxicity within initial two month of therapy. As per above studies most of the drug induced hepatic dysfunction usually occurs within the initial few weeks of intensive phase of anti-tubercular drug therapy.

Most of the patients enrolled in our study were younger and middle age groups. This may be the reason for high rate of hepatotoxicity shown in these age group patients. Because very less number of observation above 50 years of age, this may be the cause no patients developed hepatotoxicity. In present study female patients developed significant high level of liver enzymes. Although the frequency of drug induced liver injury was found to be higher in females, the severity of hepatotoxicity was not related to gender (Sinder DE 1992, Gronhagen - Riska et. al. 1978). The difference in the incidence of drug associated hepatotoxicity between male and females is mainly due to - (a) pharmacokinetic variations, probably slower biotransformation and subsequent clearance of exogenous molecules due to lower levels of microsomal enzymes; and (b) women probably being acetylators (slow acetylator enzymatic pattern shows male : female ratio of 4:1). (Marvin W. Impacts of gender ton drug response 1998). Gulbay B.E. (2006) found no age or gender difference those who develops hepatotoxicity and who had not.

This study was applied on DOTS regimen in patients of pulmonary tuberculosis. Due to time constrains and limitation of facility the obtained results may not reflect actual effects of drugs on liver functions. Further prospective longitudinal interventional randomized studies with larger sample size of different subject group are necessary recommended.

V. Conclusion

Anti-tubercular drugs given under DOTS regimen resulted in less incidence of hepatic dysfunction. In majority of cases the elevation of serum enzymes was self limiting which came down in spite of continuing therapy. The elevation of enzymes was seen mostly after four weeks of treatment. The increase activity of liver enzymes was higher in patient above 35 years of age. However no case developed into fatal hepatic failure. With the increasing incidence of tuberculosis world wise a greater number of patient are exposed to the risk of potentially effects of anti-tubercular drug. Many studies shows that incidence of hepatotoxicity is higher in daily therapy. In this study and other studies which conducted on DOTS regimen incidence of hepatic dysfunction is less.

References

[1]. Koch's Bacillus Editorial Tubercle 1982; 63: 1 – 2.
[2]. WHO (2006) Global Tuberculosis Control, Surveillance Planning Financing. WHO Report 2006.
[3]. Govt. of India (2006). Annual Report 2005 – 2006. Ministry of Health and Family Welfare New Delhi.
[4]. Govt of India (2006). TB India 2006, RNTCP status report. DOTS for all, All for DOTS, Ministry of Health and Family Welfare, New Delhi.
[5]. Sinha P.K. Sharma S.K. et. al. DOTS at a tertiary care centre in norhern India : Successes, challenges & the next stepts in tuberculosis control. Indian J. Med.Res. 123, May 2006, page 702-06.
[6]. Begum Lutfun Nahar. et. al. A comparative study on the adverse effects of two month treatment period.Bangladesh J Pharmacol 2006; 1 : 51-57.
[7]. Khalid Mahmood, Akhtar Hussain Samo, et. al. Hepatotoxicity with anti tuberculosis drugs : The risk factors. Pak J. Med. Sci. Mar. 2007; 23(1) : 33-8.
[8]. Ohno M. et. al. slow N-acetyltransferase2 genotype affects the incidence isoniazid and rifampicin - induced hepatotoxicity. Int. J. Tuberc Lung Dis. 2000; 4 : 256-61.
[9]. Hung YS. et. al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for all antibuberculosis drug induced hepatitis. Hepatology 2002; 35 : 883-9.
[10]. Rajanji Shakya, b. Subba Rao, and Bhawna Shrestha - Incidence of Hepatotoxicity due to antitubercular medicies and assessment of risk factors. The Anals of Pharmacotherapy; 2004 June, volume 38 : page 1074-78.