FREQUENCY OF RISK FACTORS FOR HEPATOTOXICITY IN PATIENTS WITH ANTITUBERCULOSIS DRUG INDUCED HEPATITIS

Nabi Rahman*, Sajjad Ali*, Muhammad Yousaf Khan*, Muhammad Umar*, Zafar Iqbal*, Anila Basit*, Zia Ullah*, Arshad Javaid*

*Department of Pulmonology, Government Lady Reading Hospital and Post Graduate Medical Institute, Peshawar - Pakistan

Adress for correspondence:
Dr. Sajjad Ali,
Department of Pulmonology, Government Lady Reading Hospital and Post Graduate Medical Institute, Peshawar - Pakistan
E-mail:drsajjadlrh@gmail.com

ABSTRACT

OBJECTIVE: To determine the frequency of risk factors for hepatotoxicity in patients presenting with anti- tuberculosis drugs induced hepatitis

METHODOLOGY: This descriptive cross sectional study included 73 admitted patients taking anti tuberculous drugs and having clinical symptoms of anorexia, nausea, vomiting and / or jaundice with raised liver functions tests. These patients were interviewed and further investigated to look for possible risk factors. Investigations apart from LFTs included complete blood picture, direct and indirect bilirubin, alkaline phosphatase, serum albumen, hemoglobin, Hepatitis B Antigen and Hepatitis C Antibodies.

RESULTS: Of 73 patients 39 were females (53.40%) and 34 males (46.60%). Mean age was 50 years with 71% (52) patients older than 35 years. Mean BMI was 18.46 kg/m^2. 67% of the patients were under weight (BMI <18.5 kg/cm^2). Mean serum albumen was 2.86 gm/dl with 87.12% Patients having serum albumin level <3.5 gm/dl. 73% Patients were having hemoglobin $\leq$ 10gm% with Mean hemoglobin of 10.25 gm%. 78.08% (57 patients) had pulmonary whereas 21.91% (16 patients) had extra pulmonary TB. 37 (64.9%) patients were sputum smear positive. Most patient (86.3%) patients had hepatotoxicity with in the intensive phase of therapy with mean of 3.92 weeks $\pm$ 2.85 SD.

CONCLUSION: ATT induced hepatotoxicity is significantly more frequent in patients with risk factors and their early identification help in pointing out patients prone to hepatotoxicity.

KEY WORDS: Hepatotoxicity; Anti-TB drugs; Tuberculosis; Risk factors.

This Article may be cited as: Rahman N, Ali S, Khan MY, Umar M, Iqbal Z, Basit A, Ullah Z, Javaid A. Frequency of risk factors for hepatotoxicity in patients with antituberculosis drug induced hepatitis. Pak J Chest Med 2015; 21(1): 04 - 9.

INTRODUCTION

Tuberculosis is one of the most prevalent diseases worldwide, especially in developing countries. It is still affecting 9.27 million new cases annually worldwide.[1] WHO has declared tuberculosis as a global emergency.[2] Pakistan ranks 4th out of 22 countries with highest tuberculosis burden worldwide and having an incidence of 275 per 100,000 populations.[3] An effective control has been achieved through widespread use of anti tuberculosis medication. Despite of their efficacy certain problems have to be faced in terms of long duration of treatment, emergence of multi drug resistant strains and certain adverse effects described to these drugs.[4] Among the adverse effects of anti tuberculosis drugs, hepatotoxicity is a well known complication, representing more than 57% of all the anti-tuberculosis drug induced reactions.[5] In Pakistan about 19.76% of the patients developed anti tuberculosis drugs (ATD) induced hepatotoxicity. It usually occurs in the initial few weeks of the intensive phase of anti tuberculosis chemotheraphy.[6] Severity of hepatotoxicty ranges from just alteration in liver enzymes, chronic hepatitis, acute hepatitis to life threating fulminant hepatic failure, carrying very high mortality until liver transplantation is done. Hepatotoxicity produced by these drugs are not truly idiosyncratic rather certain genetic

and environmental factors are attributed to produce sufficient quantity of metabolites that then cause alteration in liver function. Several factors have been identified in the causation of hepatotoxicity, among which age > 35 years, female gender, poor nutritional status, smear positivity for acid fast bacillis, wrong diagnosis, high alcohol intake and patients with hepatitis B and hepatitis C positive serology.[7-10] In Pakistan the rate of hepatotoxicity for patients taking ante tuberculosis drugs; for female gender is about 26.3%, for age > 40 years is 25.8%, for hemoglobin level < 10gm% is 52.2%, for BMI < 18.5 kg/m^2 is 91%, for albomin level < 3.5 g/dl is 27%, for alcoholics is 25%, and for sputum positive patients is 59.7%.[11] This study was planned to determine the frequency of risk factors for hepatotoxicity in patients presenting with anti-tuberculosis drug induced hepatitis. Early identification of these risk factors and their relationship with anti tuberculosis treatment may guide clinicians to educate these patients about the signs and symptoms of hepatitis, closely follow them by doing biochemical hepatic profile at regular interval of time and modify treatment regimen for patients who are at increased risk of hepatotoxicity to reduce the morbidity and mortality.

METHODOLOGY

This hospital based descriptive cross sectional study was conducted at Pulmonology department lady reading hospital Peshawar from 22 February 2010 to 21 February 2011. Data was collected by non-probability convenience sampling technique. Sample size was calculated to 73, using 25% proportion of alcoholic intake,[11] 95% Confidence level and 10% margin of error, using WHO software for sample size determination. All patients with anti tuberculosis drug induced hepatitis taking first line drugs for pulmonary tuberculosis or extra pulmonary tuberculosis and having clinical symptoms of anorexia, nausea, vomiting and / or jaundice were included in the study. Heptotoxicity was defined as inflammation of the liver caused by anti tuberculosis drugs which would be distinguished from other causes of hepatitis if there was normalization of liver enzymes level and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti-tuberculosis drugs, and presence of at least one of the following criteria.[7,11] 1) A rise to five or greater than five times the normal level of alanine aminotranseferase level. 2) A rise in the level of serum total bilirubin over 1.5 mg/dl. 3) Any increase in aminotranseferase above the normal levels together with anorexia, nausea, vomiting and jaundice. Normal maximum value in the laboratory was taken as 35 IU/L for alanine aminotranseferase and 115 IU/L for alkaline phosphatase. Following risk factors were studied: (1). Age > 35 years (2). Female gender (3). Poor Nutritional status (manifested by anemia i.e Hb⩽10gm%, albumen level <3.5 gm/dl and BMI< 18.5 kg/m^2 (4). Alcohalism i.e drinking more than six units(40 gm ethanol)/day for more than one year (5) Sputum smear positive cases (6). Wrong diagnosis {no bacteriological, histological and radiological evedince of tuberculosis} (7). Patients with hepatitis B and hepatitis C positive serology. Patients with hepatitis while taking some other hepatotoxic drugs along with anti tuberculosis drugs were excluded. Also patients with acute hepatitis whose signs and symptoms and liver function tests do not normalize after stopping anti -tuberculosis drugs for 7 days (that was an alternative diagnosis). Similarly patients taking second line drugs for multi drug resistant tuberculosis were also excluded because we could not keep these patients for 7 days in the ward due to fear of cross infection. Informed written consent was taken from all patients included in the study with no objection certificate from the ethical committee of Lady Reading Hospital Peshawar. All patients fulfilling the inclusion criteria were interviewed with a questionnaire to obtain clinical data like age, sex, alcohol intake, current clinical symptoms (anorexia, nausea, vomiting and jaundice) with duration, detailed history of tuberculosis and the drug history of not only anti tuberculosis drugs but also any drug causing hepatotoxicity. Weight and height were measured in kilogram (kg) and meter (m) respectively. All patients were subjected to complete blood picture, liver function tests (alanine aminotranseferase, serum total bilirubin, direct and indirect bilirubin, alkaline phosphatase) and serum albumen. Hemoglobin was determined by Hematology Analyzer Machine. Liver functions tests were done by using Modular Analytics (P-800 Roch) machine. Hepatitis B Antigen and Hepatitis C Antibody were done by immunochomatography (accurate kits) and positive results were confirmed by 3rd generation ELIZA using Automatic Analyzer Machine. All laboratory investigations were done in the Pathology Department while chest X-ray and ultrasound abdomen in the Radiology Department of Lady Reading Hospital, Peshawar. All patients with anti-tuberculosis drugs induced hepatitis were managed according to the standard guidelines. The above mentioned clinical, biochemical and historical data collection was documented on proforma and was analyzed statistically. Possible Confounders in the study were those patients having liver congestion secondary to right heart failure which is common in chronic lung diseases. These patients were excluded if echocardiography showed right ventricular hypertrophy or dilatation along with raised ventricular pressure. Patents with obstructive jaundice were excluded by performing ultrasound liver and abdomen. Patients with congenital and

acquired hemolytic anemia were also excluded by performing relevant investigations. Statistical analysis was performed by using SPSS version 10.0. Frequencies/Percentages were calculated for qualitative variables, while Mean ± Standard deviation were calculated for quantitative variables.

RESULTS

This study included a total of 73 patients. They were predominantly females i.e. 39 (53.40%) versus 34 (46.60%) males. Ages of the patients ranged between 15 and 80 years with an average of 50.94 yrs ± 18.778 SD among male while 14 and 80 years with an average of 45.44 years ± 19.569 SD among female. Over all 52 patients (71.23%) were older than 35 years.

Body weight of the patients showed a wide variation with 29kg and 70kg at the 2 extremes with mean body weight of 44.97kg ± 8.6281 SD. Mean height was 1.56 meter ± 6.189 SD. Body mass index ranged between 12.88 and 27.39 kg/mm with a mean of 18.46 kg/mm ± 3.3083 std. Deviation. Patients with BMI <18.5 were 49 (67.12%) and those with BMI >18.5 were 24 (32.87%).

Serum albumin level ranged between 1.30 gm/dl and 5.10 gm/dl with a mean of 2.86 gm/dl ±0.7048 SD. Deviation. Patients with albumin level <3.5 gm/dl were 64 (67.12%) versus albumin level >3.5 gm/dl were 9 (12.32%). Hemoglobin level ranged between 5.60 gm% and 15.30 gm% with a mean of 10.25 gm% ± 2.1357 std. Deviation. Patients with hemoglobin ≤ 10gm% were 54 (73.97%) while those with hemoglobin level >10 gm% were 19 (26.02%).

Baseline biochemical evaluation in levels of SGPT, AST, ALP and serum total with direct and indirect billirubins are summaries in table 1. Only three (4.10%) patients were known alcoholics and the remaining 70 (95.89%) patients were not drinking.

Patients of both pulmonary and extra pulmonary type of tuberculosis were included in the study. Out of these almost 78.08% (57 patients) had pulmonary involvement whereas the rest, 21.91% (16 patients) had extra pulmonary involvement. Among the pulmonary cases 37 (64.91%) versus 20 (35.08%) of patients were sputum smear positive. Out of 73 patients 67 (91.8%) were correctly started on ATT for tuberculosis while 6 (8.2%) were wrongly started on ATT for suspected tuberculosis.

The time interval from initiation of treatment to the onset of hepatotoxicity was also recorded. Maximum number of patients i.e 63 (86.3%) versus 10 (13.7%) developed hepatotoxicity with in the intensive phase of therapy. The minimum duration of therapy was 1 week and the maximum was 12 weeks with a mean of 3.92 weeks ± 2.85 SD. Hepatitis B positive cases were 6 (8.2%) versus 67 (91.8%) while Hepatitis C positive cases were 9 (12.3%) versus 64 (87.7%).

DISCUSSION

Tuberculosis remains a major public health problem both in developing and developed countries. Around one out of three people worldwide (i.e., approximately 1.9 billion) is infected with Mycobacterium tuberculosis. Modern short-course chemotherapy with four first line drugs combination i.e. isoniazid, rifampin, pyrazinamide and ethumbutol have proven to be highly effective against tuberculosis. However, drug-induced hepatotoxicity associated with these first-line drugs is common, as with the use of many other therapeutic agents that causing hepatotoxicity.[12,13]

This study was conducted to assess the role of age, sex, severity of the disease, nutritional status, alcoholism, wrong diagnosis and the effect of Hepatitis B and Hepatitis C positive serologies as a risk factor for ATT induced hepatotoxicity.[7-10] One prospective cohort study from Spain has shown the incidence of antituberculosis drug-induced hepatotoxicity is significantly higher in patient with these risk factors (18.2%) than in the patients without risk factors (5.8%).[14]

Table 1: BIOCHEMICAL PROFILE

Name	Number	Minimum	Maximum	Mean	Std Deviation
ALT in U/L	73	79.00	1787.0	300.1507	246.6358
AST in U/L	73	48.00	1246.0	217.9178	175.2454
Serum Bilirubin total	73	0.40	13.86	3.288	2.98209
Serum Bilirubin Direct	73	0.20	10.40	2.1208	1.95266
Serum Bilirubin Indirect	73	0.05	6.33	1.1964	1.18402
Alakaline Phosphatase	73	35.00	800	167.5342	147.787

Our study has clearly shown the higher incidence of ATT induced hepatotoxicity in female as compared to males (53.4% vs. 46.6%), a difference of 6.8% which matches with previous studies conducted.[7-15] Vulnerability of females could be due to variations in pharmacokinetics and slow acetylation enzymatic pattern, resulting in hepatotoxicity.

Older age group >35 years was affected more as compared to those having age <35 (71.23% vs. 28.76%) also strengthening the finding from previous studies.[9-16]

Nutritional status of our patients, (manifested by low HB, low serum albumin level and BMI below normal) was poor in majority of cases. Almost 74% 0f the patient were with hemoglobin levels of ≤10%, classified them in the category of moderate to severe anemia. In 49 patients (67%) BMI was below 18.5 (kg/m2) and almost 88% of the patients showed the serum albumin level below normal This poor nutritional state may be one of the risk factors of ATT induced hepatotoxicity.[7,20] The possible explanation of ATT induced hepatotoxicity in malnutrition is depletion of glutathione stores that makes one vulnerable to oxidative injuries.

Although alcohol intake is a well known risk factor for hepatotoxicity, however in our study only 3 patients were known alcoholics, reflecting either a low prevalance of alcoholism in this part of the country or supporting a few studies that denying the alcohol as a risk factor for ATT induced hepatotoxicity.[6-21]

Out of 73 cases almost 78.08% (57 patients) had pulmonary involvement whereas the rest, 21.91% (16 patients) had extra pulmonary involvement. Among the pulmonary cases, 37 (64.91%) were sputum smear positive that indicating the extensiveness of the disease as a risk factor for hepattoxicity but we have also seen in 20 patients (35.08%) who were sputum smear negative and suffered from ATT induced hepatotoxicity. Severity of the disease in sputum smear positive patients could be secondary to more tubercular bacilli load reflected by smear positive status as compared to smear negative patients.[11] In the extra pulmonary cases 15 were being treated for tuberculous pleural effusion while only one case for tuberculous lymphydinitis. The majority of exta pulmonary cases were related to the pleura, as the study was conducted in the pulmonology ward.

Out of 73 patients 6 (8.2%) were wrongly started on ATT for suspected tuberculosis in the periphery without proper investigations. Among the wrong diagnosis 5 out of 6 were extra pulmonary (pleural malignancy) while one case that was treated as milliary TB, was turned out as pneumoconiosis later on. Majority of the cases, 63 (86.30%) developed hepatotoxicity in the intensive phase of therapy i.e in the first 4 weeks which is supported by Yew and Leung, 2006,[6] Dhingra et al, 2004[27] and other studies.[11,17,28]

In this study 8.2% of the cases were turned out to be Hbs Ag positive and 12.3% of the cases were HCV antibodies positive. This is comparable to study done in Georgia in which 12% of the cases were HCV Ab positive, however only 4.3% of the cases were Hbs Ag positive.[6,9] The higher percentage of Hepatitis B positive cases in this study might be explained by the higher prevalence of Hepatitis B in this part of the world.[29]

CONCLUSION

ATT induced hepatotoxicity is significantly more frequent in patients with risk factors and can cause permanent injury and even death if not treated on time. Therefore immediate withdrawal of the offending agent is very important to arrest its development and allow liver injury to heal. Thus early identification of the risk factors that can predispose to liver injury in the patients being treated by ATT can help us in pointing out these patients.

When starting ATT especially patients with risk factors should be educated and ask to come early on the development of signs and symptoms of hepatitis. Also during intensive phase these patients should be follow up closely with clinical examination and if necessary with biochemical hepatic profile to identify hepatotoxicity at the earliest possible time.

REFERENCES

1. Donald PP, Van Halder PD. The Global burden of Tuberculosis—Combating drug resistance in difficult time. New England J Med 2009; 360:2393-5.
2. Harries A, Maher D, Graham S. TB/HIV a clinical manual, second edition. World Health Organization, Geneva 2004; 41-127.
3. Country Profile: Pakistan; Global Tuberculosis Control.WHO Report. 2014: 141-70
4. Irfan S, Hassan Q, Hasan R. Assessment of resistance in multi drug resistant tuberculosis patients. J Pak Med Assoc 2006; 56:397-400.
5. Kishore PV, Subish P, Pradipo O, Shankar PR. Pattern of adverse drug reactions experienced by tuberculosis patients in a tertiary care teaching hospital in western Nepal Pak J Pharm Sci 2008; 21:51-6.
6. Yew WW, Leung CC. Anti-tuberculosis drugs and

hepatotoxicity. Respirology 2006; 11:699-707.

7. Shakya R , Rao BS, Bhawana S. Evaluation of risk factors for antituberculosis drug-induced hepatotoxicity in Nepalese Population. Kathmandu University Journal of Science, Engineering and Technology 2008; 11:1-8.
8. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174:935–52.
9. Smink F, Hoek B, Ringer J, Altena R, Arend SM. Risk factors for acute hepatic failure during antituberculosis treatment: two cases and literature review. The Journal of Medicine Netherland 2006; 64:10.
10. Fernandez VA, Sopena B, Fernandez VJ. The influence of risk factors on the severity of anti Tuberculosis drug induced hepatotoxicity. Int J Tuberc Lung Dis 2004; 8:1499-505.
11. Mahmood K, Hussain A, Jairamani KJ, Talib A, Abbsi B, Salkeen S. Hepatotoxicity with Antituberculosis Drugs: The risk factors. Pak J Med Sci 2007; 23:33-8.
12. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf 2006; 5:231–249.
13. Fry RS, Khoshnood K, Vdovichenko E, Granskaya J, Sazhin V, Shpakovskaya L, et al. Barriers to completion of tuberculosis treatment among prisoners and former prisoners in St. Petersburg, Russia. Int J Tuberc Lung Dis 2005; 9:1027–1033.
14. Fernandez-Villar A, Sopena B, Fernandez-Villar J, color et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2004; 8:1499 - 505.
15. Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. Ann Pharmacother 2004; 38:1074–1079.
16. LoBue PA, Moser KS. Isoniazid- and rifampin-resistant tuberculosis in San Diego County, California, United States, 1993–2002. Int J Tuberc Lung Dis 2005; 9:501–506.
17. Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. Chest 2005; 128:116–123.
18. Lobato MN, Reves RR, Jasmer RM, Grabau JC, Bock NN, Shang N. Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. Chest 2005; 127:1296–1303.
19. Pedral-Sampaio DB, Alves CR, Netto EM, Brites C, Oliveira AS, et al. Efficacy and safety of Efavirenz in HIV patients on Rifampin for tuberculosis. Braz J Infect Dis 2004; 8:211–216.
20. WHO antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach 2006.
21. Agal S, Baijal R, Pramanik S, Patel N, Gupte P, Kamani P, et al. Monitoring and management of antituberculosis drug induced hepatotoxicity. J Gastroenterol Hepatol 2005; 20:1745–1752.
22. Tost JR, Vidal R, Cayla J, Diaz-Cabanela D, Jimenez A, Broquetas JM. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. Int J Tuberc Lung Dis 2005; 9:534–540.
23. Gordin FM, Cohn DL, Matts JP, Chaisson RE, O'Brien RJ. Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? Clin Infect Dis 2004; 39:561–565.
24. Gulbay BE, Gurkan OU, Yildiz OA, Onen ZP, Erkekol FO, Baccioglu A, et al. Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respir Med 2006; 10:1834–1842.
25. Aziz H, Shubair M, Debari VA, Ismail M, Khan MA. Assessment of age-related isoniazid hepatotoxicity during treatment of latent tuberculosis infection. Curr Med Res Opin 2006; 22:217–221.
26. Lee BH, Koh WJ, Choi MS, Suh GY, Chung MP, Kim H, et al. Inactive hepatitis B surface antigen carrier state and hepatotoxicity during antituberculosis chemotherapy. Chest 2005; 127:1304–1311.
27. Dhingra VK, Rajpal S, Aggarwal N, Aggarwaln JK, Shadab K and Jain SK. Adverse drug reactions observed during DOTS. J. Commun. Dis 2004; 36:251-259.
28. Pan L, Jia ZS, Chen L, Fu EQ, Li GY. Effect of antituberculosis therapy on liver function of pulmonary tuberculos patients infected with hepatitis B virus. World J Gastroenterol 2005; 11:2518–2521.

29. Mark H. Kuniholm, Jennifer, Mark, Malvina, Aladashvili et al. Risk factors and algorithms to identify hepatitis C, hepatitis B, and HIV among Georgian tuberculosis patients. Int J Infect Dis 2008;12:51–56.