Original Article

Frequency of Hepatotoxicity Caused by ATT in Pulmonary Tuberculosis

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ABSTRACT

Introduction: Tuberculosis is common disease caused by Mycobacterium Tuberculosis. Tuberculosis is one of the world's most widespread and deadly illnesses and infects an estimated 20–43% of the world's population and kills about 3 million people each year in the world. The common side effect of antituberculous drugs is hepatotoxicity. This study was carried out to determine the magnitude of hepatotoxicity caused by antituberculous drugs in patients of pulmonary tuberculosis.

Objective: To determine the frequency of hepatotoxicity caused by ATT in pulmonary tuberculosis.

Outcome measure: Frequency of hepatotoxicity

Study design: Cross sectional study

Place and Duration of Study: This study was carried out in collaboration of Department of Medicine and Department of Pulmonology, Chandka Medical College, Civil Hospital Larkana from November 2010 to May 2011.

Subjects: All consecutive sputum smears or culture positive patients or radiological evidence of active pulmonary T.B of either sex, older than 15 years of age were included in the study.

Materials and Methods: After approval of ethical committee for medical research of Shaheed Mohtarma Benazir Bhutto University Larkana, informed written consent was taken from newly diagnosed patients of pulmonary tuberculosis for participation in the study. Blood samples were taken, coded and sent for determination of liver function test. Final outcome was measured at the end of 4th week. The data was analyzed using SPSS version 17.

Results: A total of 256 patients were enrolled in this study during study period. The mean age of enrolled participants is 41.5±18.1. Of 256 patients, 132 (51.6%) were male and 124 (48.4%) were female. The male to female ratio was 1.06:1. Mean serum bilirubin was 1.5±0.7 mg/dl (Range 1.1-3.9mg/dl), the mean alanine transferase level was 34.7±11 IU/L (Range 11- 109 IU/L), aspartate transferase level was 35.4±19.3 IU/L (Range 11-112 IU/L) and alkaline phosphatase level was 150±38 IU/L (Range 95-280 IU/L).The frequency of hepatotoxicity was 51 (19.9%). Hepatotoxicity was observed in 25-35 age group was 21.7% and 56-65 years was 26%. Hepatotoxicity was observed in 23.4% female and 16.7% male.

Conclusion: It is concluded from this study that patients taking anti tuberculosis therapy are vulnerable to hepatotoxicity. Screening should be done after starting of ATT in order to avoid liver damage.

Key Words: Anti-tuberculosis therapy, hepatotoxicity, liver enzymes, Chandka medical college.

INTRODUCTION

Tuberculosis is common disease caused by Mycobacterium Tuberculosis. Tuberculosis is considered to be most important communicable disease in the world in terms of Prevalence, morbidity, mortality and problems concerning its effective control. WHO declared the tuberculosis as a global emergency[1]. Tuberculosis is one of the world's most widespread and deadly illness and infects an estimated 20-43% of the world's population and killing 3 million people worldwide each year[2-3]. Someone in the world is newly infected with tuberculosis literally, with every tick of clock (one person per second)[4-5].

According to the World Health Organization's (WHO's) Global Tuberculosis Control 2009, Pakistan ranks eighth on the list of 22 high-burden tuberculosis (TB) countries in the world[6]. In 2007, an estimated 297,108 people in Pakistan (primarily adults in their productive years) developed TB. The case detection rate for Pakistan rose from 13 percent in 2002 to 67 percent in 2007, close to WHO's target of 70 percent[6]. The incidence and prevalence of all forms of tuberculosis in Pakistan is 181 and 223 per 100,000 persons per year respectively, and 29% of these die in a year[6]. The steep rise in case detection and the number of TB cases reported each year since 2000 is the result of nationwide efforts to increase involvement of private practitioners and community volunteers in identifying and referring TB suspects[6-7].

An effective control has been achieved by the widespread use of anti tuberculosis drugs. However, despite their efficacy, superadded problems have to be faced in terms of long duration of treatment, emergence of MDR strains and certain adverse effects ascribed to these drugs. Among these adverse effects hepatotoxicity is a well-known complication of Anti Tuberculosis Therapy (ATT) causing 19.7% cases[8-10]. The severity ranges from alteration in liver enzymes, chronic active hepatitis and picture of acute hepatitis, occasionally complicated by acute liver failure carrying very high mortality unless transplanted. It is common

with Isoniazid especially when given in combination with Rifampicin and Pyrazinamide. Ten to 20 percent of patients receiving Isoniazid as a single agent for prophylaxis against tuberculosis may have increased serum alanine and aspartate aminotransferase levels, but only 1 percent have hepatic necrosis severe enough to require the withdrawal of the drug[9-12]. Its incidence is reported to be lower i.e. 3-4% from developed countries as compared to 8-39% in the developing countries with the same regimens[13-16]. The clinical, biochemical and histopathological features of anti-tuberculosis induced hepatotoxicity are indistinguishable from that of viral hepatitis[17].

It has been postulated that hepatotoxicity induced by ATT is not truly idiosyncratic in essence. Rather certain genetic and environmental factors are attributed to coincide to produce sufficient quantity of toxic metabolites that then cause varied alterations in liver functions. ATT inducible cytochrome P-450 2E1 (cyp2E1) is constitutively expressed in the liver. Recent studies show that polymorphism of the N-acetyltransferase2 (NAT2) genes and glutathione-s transferases (GST) are the two major susceptibility risk factors for ATT induced hepatotoxicity[18-19].

MATERIALS AND METHODS

This is the cross sectional study, which was carried out in collaboration of Department of Medicine and Department of Pulmonology, Chandka Medical College, Civil Hospital Larkana. This study was done during November 2010 to May 2011. Sample size was calculated for population, proportion with specified absolute precision method. Assuming the anticipated prevalence of hepatotoxicity in tuberculosis patients in Pakistan at 19.6% (P), keeping the confidence interval (1-α) at 95% and absolute precision (d) set at 5%, the sample size is estimated to be as **256** patients by using WHO sample calculation software by above parameters.

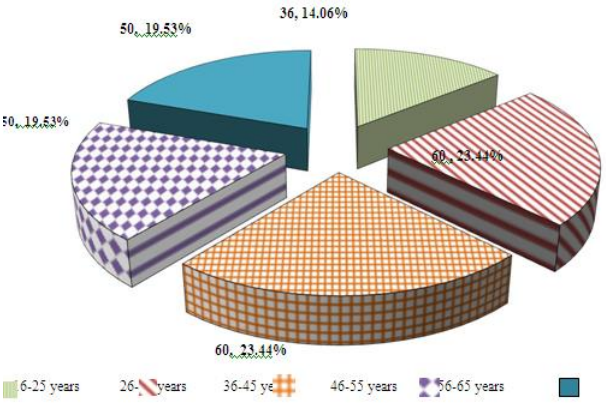
All consecutive sputum smears or culture positive patients or radiological evidence of active pulmonary T.B of either sex older than 15 years were included in study.

All patients above the age of 65 years with previous history of anti-tuberculosis therapy and evidence of chronic liver disease as viral hepatitis, alcoholic hepatitis, drugs and auto immune disorders were excluded from study. Patients suffering from chronic kidney disease, pregnant women and patients suffering from hemolytic disorders were also excluded from the study.

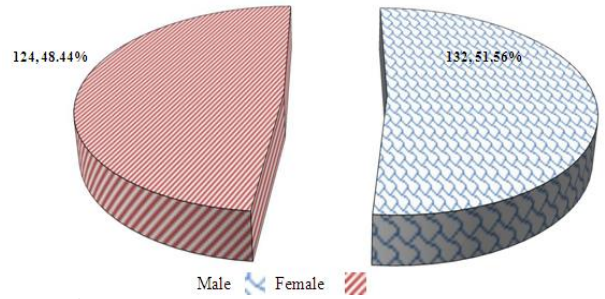
After approval of ethical committee for medical research of Shaheed Mohtarma Benazir Bhutto University Larkana, informed written consent was taken from newly diagnosed patients of pulmonary tuberculosis for participation in the study. Blood samples were taken, coded and sent for determination of liver function test (serum aspartate transferase "AST", serum alanine transferase "ALT", alkaline phosphatase "ALK" and serum Bilirubin) before starting anti-tuberculosis therapy and then weekly for first four weeks. Any patient who developed hepatotoxicity during course of therapy was evaluated to exclude other potential causes, such as viral hepatitis. Increased in serum amino transferases or alkaline phosphatase or serum bilirubin within 4 weeks of start of anti tuberculosis therapy, was labeled as positive for anti-tuberculosis therapy induced hepatotoxicity. Final outcome was measured at the end of 4th week. The data was collected and recorded to predesigned Proforma by the principle**.** The data was entered and analyzed using SPSS software version 17.0. Continuous variables as age, serum AST, serum ALT, serum ALK and serum Bilirubin was presented in mean ± SD (Standard Deviation). Categorical response variable as gender, age and presence or absence of hepatotoxicity was presented in frequencies and percentages for data presentation. Stratification was done with regard to age and sex to see effect of these variables on outcome.

RESULTS

A total of 256 patients were enrolled in this study during study period. The mean age of enrolled participants is 41.5±18.1 (Graph 1). Of 256 patients, 132 (51.6%) were male and 124 (48.4%) female. The male to female ratio was 1.06:1 (Graph 2). The descriptive of liver enzymes was summarized in table 1. Mean serum bilirubin was 1.5±0.7 mg/dl (Range 1.1-3.9 mg/dl), the mean alanine transferase level was 34.7±11 IU/L (Range 11-109 IU/L), aspartate transferase level was 35.4±19.3 IU/L (Range 11-112 IU/L) and alkaline phosphatase level was 150±38 IU/L (Range 95-280 IU/L).The frequency of hepatotoxicity was 51 (19.9%) (Graph 3). Stratified analysis based on age and sex was summarized in tables 2-3. Hepatotoxicity was observed in 25-35 age group was 21.7% and 56-65 years was 26%. Hepatotoxicity was observed in 23.4% female and 16.7% male.

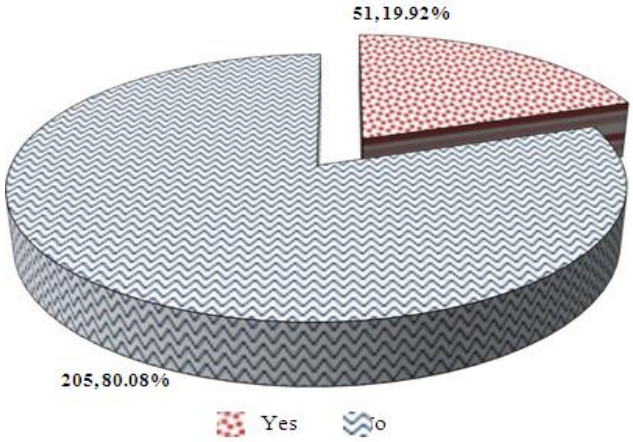


Graph No.1: Age distribution of enrolled participants (n=256)



Male to female ratio was 1.06:1

Graph No.2: Sex distribution of enrolled participants (n=256)



Graph No.3: Frequency of hepatotoxicity in enrolled participants (n=256)

Table 1: Descriptive of serum bilirubin and liver enzymes (n=256)

Variables	Means	SD	Range
Serum Bilirubin	1.5	0.7	(1.1-3.9 mg/dl)
Alanine Aminotransferase	34.7	11	(11-109 IU/L)
Aspartate Aminotransferase	35.4	19.3	(11-112 IU/L)
Alkaline phosphatase	150	38	(95-280 IU/L)

Table 2: Stratification of hepatotoxicity based on age

Hepatotoxicity	16-25 Years (n-36)	26-35 Years (n-60)	36-45 Years (n-60)	46-55 Years (n-50)	56-65 Years (n-50)	Total
Yes	19.4%	21.7%	11.7%	22%	26%	19.9%
No	80.6%	78.3%	88.3%	78%	74%	80.1%

Table No.3: Stratification of hepatotoxicity based on sex

Hepatotoxicity	Male (n-132)	Female (n-124)	Total
Yes	16.7%	23.4%	19.9%
No	83.3%	76.6%	80.1%

DISCUSSION

Tuberculosis constitutes major public health challenge, which is declared as global emergency by WHO[3]. Tuberculosis is a treatable endemic disease in Pakistan. Antituberculous therapy is the basic approach to control tuberculosis, but multiple antituberculous drug regimens exposing patients to liver damage[2,10]. Drug induced liver injury is a problem of increasing significance but has been a long-standing concern in the treatment of tuberculous infection. The liver has a central role in drug metabolism and detoxification and is consequently vulnerable to injury. The pathogenesis and type of drug induced liver injury are presented, ranging from hepatic adoption to hepatocellular injury. The knowledge of the metabolism of antituberculous medications and of the mechanism of hepatotoxicity is incomplete. Understanding of antituberculous drugs induced liver injury has been hampered by differences in study populations, definitions of hepatotoxicity, and monitoring and reporting practices[20]. In this study, the mean age of patients suffering from deranged liver enzymes was 41.5 years. This result was similar to mean age reported AKbri MZ[2], Yee D[12] i.e. 43.5 years and 40.3 years respectively, whereas vidal pla R[21], showed no specific relation with age. In this study female gender had got increased frequency of deranged liver enzymes, these results were comparable with Shakya R[10], Yee D[12] where as not comparable with Akbri MZ[2], Vidal pla R[21], where the gender had not influenced the results. In this study proportion of patients with deranged liver enzymes recorded 19.9%, while it was recorded as 40% by shakya R[10], 16.5% by vidal pla R[21], 16% by Akbri MZ[2] and 3% by Yee D[12], in their studies. The sample sizes were different in all these studies except Shakya R[10] that had studied patients those were comparable with our study.

In this study as well as in all other studies mentioned above, the therapy was continued despite the deranged liver enzymes. After two months in all studies patients with deranged liver enzymes had improved gradually.

None of the patients enrolled in our study, had deranged liver enzymes more than three times of the upper limit of normal level. This statement is also in agreement with all above mentioned studies.

There are few limitations in this study; first, this was a hospital based study not representative of population; second, in this study there was no comparative group. This study suggests that abnormalities of liver function are most likely to occur within the first eight weeks of treatment and during this period liver enzymes should be checked on four weekly bases, but monitoring the enzymes after this period should not be that much aggressive.

CONCLUSION

It is concluded that frequent monitoring of liver enzymes is essential to screen for the early liver damage due to antituberculous therapy. However mild increase in liver enzymes (less than three times of the upper limit of the normal level) doesn't warrant cessation of antituberculous therapy.

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