Drugs are an important cause of liver injury. Approximately 75% of the idiosyncratic drug reactions result in liver transplantation and death[2,3]. Drug induced hepatic injury is the most common reason cited for withdrawal of an approved drug. The manifestations of drug induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure[4].

WHO has declared that tuberculosis is a global emergency. An effective control has been achieved by the widespread use of antitubercular drugs. But the antitubercular therapy (ATT) causes hepatotoxicity[5-7]. Early recognition of ATT induced hepatotxicity with immediate withdrawal of offending agent is very important to arrest its development. British Thoracic Society suggests that if there is a rise in Alanine Amino Transferase (ALT) and/or Aspertate Amino Transferase (AST) to greater than 3 times normal, or a rise in bilirubin, or if the patient shows clinical symptoms of hepatitis then drugs should be stopped and reintroduced sequentially when these parameters fall to previous levels[8]. Patients of tuberculosis usually belong to poor socioeconomic status and they cannot afford regular Liver Function Tests (LFTs). Close monitoring of the patient's physical condition can be done in such situations. Physician must be vigilant in identifying drug related liver injury because early detection can decrease the severity of hepatotoxicity if the drug is discontinued[9].

The current recommended treatment regimens for tuberculosis involve drugs which are potentially hepatotoxic[10]. Certain genetic and environmental factors are attributed to coincide to produce sufficient quantity of toxic metabolites that then cause varied alterations in liver functions[11].

The underlying mechanisms of ATT induced hepatotoxicity and the factors predisposing to its development are not clearly understood. The age, sex, poor nutritional status, chronic alcoholism, pre-existing liver disease, hypoalbuminaemia, advanced tuberculosis, acetaminophen, inappropriate use of drugs and acetylator status have all been incriminated as possible predisposing factors in earlier studies[12]. In this perspective, we designed this study to know the possible risk factors for the development of drug induced hepatotoxicity and the incidence of hepatic damage and overt hepatitis in patients receiving antitubercular treatment as per National Tuberculosis Control Programme (NTP) strategy.

MATERIALS AND METHODS

This cross sectional prospective study based on purposive sampling technique was conducted in department of Biochemistry of Chittagong Medical College, Chittagong during the period of July 2010 to January 2011. In this study, one hundred newly diagnosed pulmonary tuberculosis patients, both male and female, attending the medicine outpatient department, admitted in Chittagong Medical College Hospital and DOTS center in the hospital, were included. Patients who were diagnosed to have pulmonary tuberculosis with sputum smear positive for the first time were included.

Exclusion criteria

1. Patients with extra pulmonary tuberculosis.

2. Patients of pulmonary tuberculosis who were defaulters, treatment failure cases and multidrug resistance cases.

3. Patients with abnormal baseline liver function tests.

4. Patients with positive HbsAg, HIV, Anti HCV Ab, cirrhosis of liver, acute viral hepatitis and/or gastrointestinal, renal or cardiac diseases.

Detailed history of all subjects was taken and thorough clinical examination was done, including measurement of height and weight and calculation of BMI. History of high alcohol intake was noted. Severity of pulmonary tuberculosis (PTB) was assessed by chest radiography. Serum albumin level was also measured.

Before initiation of treatment, baseline investigations for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum bilirubin were done. All these investigations were repeated after 2-month treatment with 4-drugs regimen (isoniazid, rifampicin, pyrazinamide and ethambutol). Patients with high levels of these parameters on repeat tests were categorized as having hepatotoxicity. Hepatotoxic patients were then evaluated for various factors.

Cut off values of the enzymes:

AST:

Men	up to	41 U/L	……	At 37^{o} c
Women	up to	32 U/L	……..	At 37^{o}c

ALT:

Men	up to	45 U/L	……	At 37^{o} c
Women	up to	32 U/L	……..	At 37^{o}c

Serum bilirubin:

0.2 --------1.2 mg/dl

Statistical analysis

Chi-square test was done to see the association of hepatotoxicity with different variables. p value <0.05 was considered significant.

RESULTS

In the present study, we enrolled 100 patients who were diagnosed to have pulmonary tuberculosis for the first time. These patients were given DOTS therapy Four Fixed Dose Combination (4FDC)) as per National Tuberculosis Program (NTP) guidelines. All patients had normal liver function tests before the initiation of therapy. Liver function tests were repeated at 8th week of the treatment to note the elevation in serum bilirubin and serum ALT and AST levels to find out the antituberculosis treatment induced hepatotoxicity. According to these investigation results we found that among 100 subjects 20 patients developed hepatotoxicity.

The time when pain start

This study showed that pain was aggravated during work among the most respondents (46.9%), and 14.3% respondents had continuous pain.

Table I : Biochemical profile of patients with hepatotoxicity (n=20)

	Mean ALT U/L	Mean AST U/L	Mean total bilirubin mg/dL
Basal level	32.5	30.0	0.7
Peak level	210.5	205.5	4.9
After recovery	85.7	63.4	1.1

Table II: Association of age and BMI with hepatotoxicity (n=100)

Variables	Number	Percentage	χ^2 value	p value
Age in years				
50-65 (n=50)	17	34	11.4	<0.001
15-49 (n=50)	03	06		
BMI				
>18.5 (n=30)	08	27	1.0	>0.05
<18.5 (n=70)	12	17		

Table III: Association of pretreatment disease severity, alcohol consumption and serum albubin status of patients with hepatotoxicity (n=100)

Variables	Number	Percentage	χ^2 value	p value
Severity of disease (PTB)*				
Not severe (n=65)	04	06	22.2	<0.001
Severe (n=35)	16	46		
High alcohol intake				
Yes (n=26)	16	62	37.89	<0.001
No (n=74)	04	05		
Serum albumin (g/dL)				
?3.5 (n=44)	02	05	11.71	<0.001
<3.5 (n=56)	18	32		

* Severity of disease was assessed before treatment initiation by chest radiography

These results indicate that advancing age is an independent risk factor for drug induced hepatotoxicity. The patients in the age group of >50 years were found 5.67 times higher to have hepatotoxicity as compared to the patients in the age group of <50 years (p<0.001).

In this study 27% patients in BMI >18.5 group developed Anti Tuberculosis Therapy (ATT)induced hepatotoxicity whereas in BMI <18.5 group 17% developed ATT induced hepatotoxicity (p>0.05).

The patients who presented with radiologically severe Pulmonary Tuberculosis (PTB) showed higher drug induced hepatotoxicity than patients presenting with radiologically milder disease (p<0.001). The patients with history of high alcohol intake were also found to have higher ATT induced hepatotoxicity as compared to non-alcoholics while receiving ATT (p<0.001).

The patients presenting with pre-treatment hypoalbuminemia were found to have higher ATT induced liver damage than patients presenting with normal serum albumin levels (p<0.001).

In this study 20 (20%) cases showed the evidence of ATT induced liver damage in the form of elevation of serum bilirubin, serum AST and ALT levels above normal. Among them 5 (5%) cases developed overt Drug Induced Hepatotoxicity (DIH) as defined above and remaining 15 (15%) cases had asymptomatic elevation of serum ALT, AST and bilirubin levels. The remaining 80 (80%) cases did not show any significant change in their serum bilirubin and/or enzyme levels as compared to pre-treatment levels.

DISCUSSION

Isoniazid, rifampicin and pyrazinamide have been observed to have hepatotoxic potential. DIH is an important and commonly encountered adverse effect with anti-TB treatment[13,14]. Several types of drug induced liver damage have been described. Mechanisms of drug induced hepatotoxicity include idiosyncratic damage, dose dependent toxicity, induction of hepatic enzymes, drug induced acute hepatitis, allergic reactions. Specific patterns of hepatic damage include disruption of intracellular calcium homeostasis, cholestatic damage, interruption of transport pumps and loss of villous processes, reactions involving cytochrome p-450 system, activation of apoptotic pathways and programmed cell death and inhibition of mitochondrial function. So early recognition of risk factors with close follow-up of patients receiving ATT and subjecting them to repeated liver function tests will significantly reduce morbidity and mortality and improve the compliance of the patients receiving ATT.

LIMITATIONS OF THE STUDY

The sample size was calculated excluding HIV, HBsAg and Anti-HCV antibody positive patients. So, it is not representing the whole population. Moreover, since the study was conducted only in urban health institutions in one city there might be a problem of representing the whole country.

CONCLUSION

In the present study, frequency of DIH in patients receiving DOTS therapy is 20%. Patients in the age group of >50 years, patients presenting with radiologically severe form of PTB, alcoholics and hypoalbuminics were found to have higher DIH. So, from the findings in our study we can conclude that advancing age, history of high alcohol intake, radiologically severe form of PTB and pretreatment hypoalbuminemia are important risk factors except low BMI for development of ATT induced hepatotoxicity in Bangladeshi population.

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DISCLOSURE

All the authors declared no competing interest.

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