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Original Article

Assessment of the hepatotoxicity induced by anti-tuberculosis drugs in tuberculosis subjects undergoing treatment

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ABSTRACT

Background: One of the major health concerns reported in the Indian subjects is Tuberculosis which also poses a high burden on the economic and social status of India along with the healthcare sector. With the implementation of DOTS and other treatment strategies, there is control in India for tuberculosis. However, one of the major drawbacks associated with anti-tubercular drugs is hepatotoxicity.

Aims: The present clinical study was conducted to assess the hepatotoxicity frequency in subjects taking anti-tubercular drugs and to assess the methods, risk factors, and predictive factors in subjects developing hepatotoxicity with anti-tubercular drugs.

Materials and methods: The present prospective clinical study screened 140 subjects, and 120 subjects were finally included in the study as 5 subjects died due to hepatic and extra-hepatic reasons and 15 did not turn for follow-up. The data was collected for hepatotoxicity and were analyzed for the formulation of the result.

Results: Among 120 study subjects, antituberculosis drug-induced hepatotoxicity (AIH) was seen in 3.33% (n=4) study subjects where there were 2.5% (n=3) males and 0.83% (n=1) females with antituberculosis drug-induced hepatotoxicity (AIH). In the age range, 2.5% (n=3) subjects were in the age range of 20-39 years and 0.83% (n=1) subjects in the age range of 40-59 years. All 4 study subjects with antituberculosis drug-induced hepatotoxicity (AIH) were in the BMI range of <18. On assessing the clinical features in the study subjects, nausea was seen in 5 study subjects had nausea where 80% (n=4) subjects had AIH, 4 subjects had vomiting where 75% (n=3) subjects had AIH, 2 subjects had ascites where 100% (n=1) had AIH, 5 subjects had jaundice where 80% (n=4) had AIH, 1 subject had edema where 100% (n=1) had AIH along with edema, 1 subject had encephalopathy where 100% (n=1) subject had AIH and encephalopathy both, and 1 subject had coagulopathy where all 100% (n=1) had coagulopathy with AIH.

Conclusion: The present study concludes that a low prevalence of hepatotoxicity is seen in subjects with tuberculosis, and hence, RNTCP and DOTS can be successfully implemented in subjects with tuberculosis without restricting much for hepatotoxicity.

Keywords: Anti-tubercular drugs, DOTS, Hepatotoxicity, Tuberculosis.

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INTRODUCTION

Hepatotoxicity is the injury to the liver caused by chemicals and/or drugs, and is the most vital factor during chemotherapeutic management of various diseases, and also of post-marketing drug withdrawal. Hence, reducing/ preventing hepatotoxicity along with its understanding is a vital factor involving the treating personnel and the drug developers. High sensitivity to drugs is seen in the Liver since the liver has a major role in the biotransformation of the drugs along with other foreign substances before they could reach their site of action in a harmless form. The hepatotoxic action of drugs is dependent on both acquired as well as genetic factors along with being the most unpredictable and infrequent drug reactions.[1]

The significance for hepatotoxicity both for the drugs and subject is different with the varied presentation with an outcome spectrum existence varying from the mild asymptomatic elevation of enzymes to progressive and life-threatening liver disease. Prompt withdrawal and early identification of the drug causing hepatotoxicity is the only vital need in the affected subjects. Adverse drug reactions are usually not identified in the early stage, as they lack any peculiar characteristic and no reliable biomarker is identified that can identify the liver toxicity due to drugs. Biochemically, morphologically, and clinically, hepatotoxicity resembles the liver disease caused by other etiologies. Different biochemical tests may also show abnormal values in hepatotoxicity subjects similar to the liver injury. Liver injury is generally

identified with abnormal liver tests with more than twice the increase in the upper limit for serum bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) levels.[2]

Drug-induced hepatotoxicity is most commonly caused by acetaminophen in western countries, whereas, in India, anti-tubercular drugs constitute the most common cause of drug-induced liver disease, especially the INH (Isoniazid). The clinical picture of drug-induced liver disease has varied expression from asymptomatic abnormalities in the levels of liver enzymes that that usually disappear with the drug withdrawal or continuation to acute hepatitis which is symptomatic that often proceeds to fulminant liver failure. The hepatitis incidence caused by the anti-tubercular drugs varies from 1% to 36% based on the various definitions and the drug regimens used. Various risk factors attributed to the increased risk for drug-induced hepatotoxicity are existing chronic liver diseases, acetylator status, advanced age, and alcohol consumption. Various pathogenesis has been proposed behind this hepatotoxicity, however, the exact mechanism behind this hepatotoxicity is not understood well and remains largely unclear.[3]

In the recent past in India, large change is being seen in the treatment approach for tuberculosis with subjects are being given the standard drugs and with the intermittently observed therapy, DOTS. In the previous literature, very little data has focused on the hepatotoxicity incidence using this regime. DOTS was introduced for tuberculosis treatment for getting better compliance, it is still unclear if the hepatotoxicity prevalence differs in the DOTS regimen compared to the daily regimen used earlier.[4] For the present study, in subjects of both pulmonary and extra-pulmonary tuberculosis, taking anti-tubercular drugs, the values of bilirubin as >2mg/dl and serum ALT as more than 2 times of the normal value of 0-40 IU/L were considered as liver disease, provided the pre-treatment values in these subjects were normal. Hence, the present clinical study was conducted to assess the hepatotoxicity frequency in subjects taking anti-tubercular drugs and to assess the methods, risk factors, and predictive factors in subjects developing hepatotoxicity with anti-tubercular drugs.

MATERIALS AND METHODS

The present prospective clinical study was conducted to assess the hepatotoxicity frequency in subjects taking anti-tubercular drugs and to assess the methods, risk factors, and predictive factors in subjects developing hepatotoxicity with anti-tubercular drugs. The study was carried out at Department of TB & Chest, Chhatrapati Shivaji Maharaj Hospital and Rajiv Gandhi Medical College, Kalwa, Thane, Maharashtra from February 2011 to December 2011. The study population was comprised of the subjects visiting the department of Pulmonary Medicine of the Institute.

The present study screened 140 subjects, and 120 subjects were finally included in the study as 5 subjects died due to hepatic and extra-hepatic reasons and 15 did not turn for follow-up. Based on RNTCP (Revised National Tuberculosis Control Program) the subjects were treated with DOTS (Directly Observed Treatment, Short-course). Biochemically and clinically, ADR (adverse drug reactions) were noted, and accordingly, the subjects were followed-up. After explaining the detailed study design, informed consent was taken from all the subjects in both written and verbal form.

The inclusion criteria for the study were subjects having pulmonary or extra-pulmonary tuberculosis and were treated with DOTS under RNTCP guidelines without considering their status, and the subjects who were willing to participate in the study. The exclusion criteria for the study were subjected less than 13 years of age, subjects on medications that can lead to hepatotoxicity, alcoholic liver disease, subjects with altered therapy, who did-not follow DOTS, and clinically decompensated liver diseases.

For the present study, in subjects of both pulmonary and extra-pulmonary tuberculosis, taking anti-tubercular drugs, the values of bilirubin as >2mg/dl and serum ALT as more than 2 times the normal value of 0-40 IU/L or both were considered as liver disease. Also, in all the subjects, signs and symptoms of hepatotoxicity should be improved after drug discontinuation and liver enzymes should be within the normal limits. For all the study subjects, ALT was determined at baseline, 15th day, 30th day, and 60th day of the study. Additional assessment of serum ALT and bilirubin was done if any subject developed adverse reactions like oliguria, skin rashes, jaundice, or vomiting during the first two months of the anti-tubercular treatment.

In subjects with symptomatic hepatotoxicity, ELISA, HIV1 and 2, IgM anti HEV, IgM anti HAV, anti HCV, IgM anti-HbcAg, HbsAg, serum ceruloplasmin, serum albumin, serum bilirubin, and serum ALT was assessed.

In selected cases, liver biopsy was planned, and in subjects increased bilirubin or serum ALT, drugs were continued followed by assessment both biochemically and clinically. The collected data were subjected to the statistical evaluation and the data were expressed in percentage and number, and mean and standard deviation.

RESULTS

The present prospective clinical study was conducted to assess the hepatotoxicity frequency in subjects taking anti-tubercular drugs and to assess the methods, risk factors, and predictive factors in subjects developing hepatotoxicity with anti-tubercular drugs. The present study included 120 subjects from both genders with pulmonary or extra-pulmonary tuberculosis. The demographic characteristics of the study subjects are listed in Table

1. It was seen that majority of the study subjects were within the age range of 20-39 years with 49.16% (n=59) subjects followed by 28.3% (n=34) subjects in age of 40-59 years, 13.3% (n=16) subjects in 13-19 years, and 9.16% (n=11) subjects in 60-79 years age group. There were 63.3% (n=76) males and 36.6% (n=44) females in the present study. Concerning BMI, 50% (n=60) subjects had BMI of <18, 43.3% (n=52) had BMI of 18-25, and 6.66% (n=8) had BMI of 25-29.9 (Table 1).

Among 120 study subjects, antituberculosis drug-induced hepatotoxicity (AIH) was seen in 3.33% (n=4) study subjects where there were 2.5% (n=3) males and 0.83% (n=1) females with antituberculosis drug-induced hepatotoxicity (AIH). In the age range, 2.5% (n=3) subjects were in the age range of 20-39 years and 0.83% (n=1) subjects in the age range of 40-59 years. All 4 study subjects with antituberculosis drug-induced hepatotoxicity (AIH) were in the BMI range of <18 as shown in Table 2.

On assessing the clinical features in the study subjects, nausea was seen in 5 study subjects had nausea where 80% (n=4) subjects had AIH, 4 subjects had vomiting where 75% (n=3) subjects had AIH, 2 subjects had ascites where 100% (n=1) had AIH, 5 subjects had jaundice where 80% (n=4) had AIH, 1 subject had edema where 100% (n=1) had AIH along with edema, 1 subject had encephalopathy where 100% (n=1) subject had AIH and encephalopathy both, and 1 subject had coagulopathy where all 100% (n=1) had coagulopathy with AIH as depicted in Table 3.

S. No	Characteristics	Percentage (%)	Number (n)
1.	**Age range (years)**		
a)	13-19	13.3	16
b)	20-39	49.16	59
c)	40-59	28.3	34
d)	60-79	9.16	11
2.	**Gender**		
a)	Males	63.3	76
b)	Females	36.6	44
3.	**BMI (kg/m2)**		
a)	<18	50	60
b)	18-25	43.3	52
c)	25-29.9	6.66	8

Table 1: Demographic characteristics of the study subjects

S. No	AIH parameters	Percentage (%)	Number (n)
1.	**Total subjects**	3.33	4
2.	**Gender**		
3.	Males	2.5	3
4.	Females	0.83	1
5.	**Age range (years)**		
a)	13-19	-	-
b)	20-39	2.5	3
c)	40-59	0.83	1
d)	60-79	-	-
6.	**BMI (kg/m2)**		
a)	<18	3.33	4
b)	18-25	-	-
c)	25-29.9	-	-

Table 2: AIH characteristics in the study subjects

S. No	Variable	Total subjects	Subjects with AIH n (%)
1.	**Coagulopathy**	1	1 (100)
2.	**Encephalopathy**	1	1 (100)
3.	**Edema**	1	1 (100)
4.	**Jaundice**	5	4 (80)
5.	**Ascites**	2	1 (100)
6.	**Vomiting**	4	3 (75)
7.	**Nausea**	5	4 (80)

Table 3: Clinical features in the study subjects

DISCUSSION

The present prospective clinical study was conducted to assess the hepatotoxicity frequency in subjects taking anti-tubercular drugs and to assess the methods, risk factors, and predictive factors in subjects developing hepatotoxicity with anti-tubercular drugs. The present study included 120 subjects from both genders with pulmonary or extra-pulmonary tuberculosis. The demographic characteristics of the study subjects are listed in Table 1. It was seen that majority of the study subjects were within the age range of 20-39 years with 49.16% (n=59) subjects followed by 28.3% (n=34) subjects in age of 40-59 years, 13.3% (n=16) subjects in 13-19 years, and 9.16% (n=11) subjects in 60-79 years age group. There were 63.3% (n=76) males and 36.6% (n=44) females in the present study. Concerning BMI, 50% (n=60) subjects had BMI of <18, 43.3% (n=52) had BMI of 18-25, and 6.66% (n=8) had BMI of 25-29.9. These demographics were comparable to the studies of Rolla VC et al[5] in 2006 and Tost JR et al[6] in 2005 where authors assessed subjects with comparable demographics as in the present study.

Among 120 study subjects, antituberculosis drug-induced hepatotoxicity (AIH) was seen in 3.33% (n=4) study subjects where there were 2.5% (n=3) males and 0.83% (n=1) females with antituberculosis drug-induced hepatotoxicity (AIH). In the age range, 2.5% (n=3) subjects were in the age range of 20-39 years and 0.83% (n=1) subjects in the age range of 40-59 years. All 4 study subjects with antituberculosis drug-induced hepatotoxicity (AIH) were in the BMI range of <18. These results were consistent with the findings of Chowdhury A et al[7] in 2003 and Warmelink I et al[8] in 2011 where authors reported similar hepatotoxicity parameters as in the present study y the authors.

For the assessment of the clinical features in the study subjects, nausea was seen in 5 study subjects had nausea where 80% (n=4) subjects had AIH, 4 subjects had vomiting where 75% (n=3) subjects had AIH, 2 subjects had ascites where 100% (n=1) had AIH, 5 subjects had jaundice where 80% (n=4) had AIH, 1 subject had edema where 100% (n=1) had AIH along with edema, 1 subject had encephalopathy where 100% (n=1) subject had AIH, and encephalopathy both, and 1 subject had coagulopathy where all 100% (n=1) had coagulopathy with AIH. These results were in agreement with the studies of Kumar R et al[9] in 2010 and Devarbhavi H et al[10] in 2010 where authors reported the clinical features comparable to the present study in subjects with AIH as in the present study.

CONCLUSION

Within its limitations, the present study concludes that a low prevalence of hepatotoxicity is seen in subjects with tuberculosis, and hence, RNTCP and DOTS can be successfully implemented in subjects with tuberculosis without restricting much for hepatotoxicity. The present study had a few limitations including a small sample size, shorter monitoring period, and geographical area biases. Hence, more longitudinal studies with a larger sample size and longer monitoring period will help reach a definitive conclusion.

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