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EVALUATING TECHNIQUES, RISK FACTORS, AND PREDICTIVE VARIABLES FOR HEPATOTOXICITY CAUSED BY ANTI-TUBERCULOSIS DRUGS IN TUBERCULOSIS MANAGEMENT

Dr Madhuri Gadela,[1*] Dr Raghavendra Verma,[2] Dr Amandeep Singh Arneja,[3] Dr Laxmi Kanta Mohanty[4]

[1*]MBBS, DTCD, DNB, Assistant Professor, Department of Respiratory Medicine, Shri Shankaracharya Institute of Medical Sciences, Bhilai, Durg, Chhattisgarh

[2]MBBS, DNB, Assistant Professor, Department of Respiratory Medicine, Shri Shankaracharya Institute of Medical Sciences, Bhilai, Durg, Chhattisgarh

[3]MBBS, 3rd year PG, Department of Respiratory Medicine, Shri Shankaracharya Institute of Medical Sciences, Bhilai, Durg, Chhattisgarh

[4]MBBS, MD, Professor, Department of Respiratory Medicine, Shri Shankaracharya Institute of Medical Sciences, Bhilai, Durg, Chhattisgarh

Address for correspondence
Dr Madhuri Gadela
Email id: madhuri.g1005@gmail.com

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ABSTRACT

Background: Tuberculosis is a serious health problem that has been observed in Indian subjects. It is also a big strain on the country's social and economic standing as well as the healthcare system. In India, TB is managed well thanks to the use of DOTS and NTEP treatment Hepatotoxicity, however, is one of the main side effects of anti-tubercular medications.

Aim: The current clinical study's objectives were to determine the prevalence of hepatotoxicity in patients receiving anti-tubercular medications as well as the techniques, risk factors, and predictive variables for individuals experiencing hepatotoxicity from anti-tubercular medications.

Methods: After screening 140 participants for the current prospective clinical trial, 120 participants were ultimately included to the study, since 5 participants passed away from hepatic and extrahepatic causes, and 15 participants were lost to follow-up. The hepatotoxicity data was gathered and examined in order to formulate the conclusion.

Results: 3.33% (n=4) of the 120 research participants had antituberculosis drug-induced hepatotoxicity (AIH), with 2.5% (n=3) of the men and 0.83% (n=1) of the females experiencing this side effect. 2.5% (n=3) of the participants fell between the ages of 20 and 39, while 0.83% (n=1) of the patients fell between the ages of 40 and 59. The BMI range for all four research participants experiencing antituberculosis drug-induced hepatotoxicity (AIH) was less than 18.

After evaluating the clinical characteristics of the research participants, it was observed that 5 study subjects experienced nausea (80%; n = 4); 4 subjects experienced vomiting (n = 3); 2 subjects experienced ascites (n = 1); 5 subjects experienced jaundice (n = 4); 1 subject experienced edoema (n = 1); 100% (n = 1) experienced both encephalopathy and AIH; and 1 subject experienced coagulopathy (n = 1) with 100% of the subjects experiencing coagulopathy and AIH.

Conclusion: The current study comes to the conclusion that patients with TB have a low prevalence of hepatotoxicity, meaning that NTEP and DOTS may be successfully used in these patients without placing too much restriction on hepatotoxicity.

Keywords: Anti-tubercular drugs, DOTS (Directly Observed Treatment, Short-course), Hepatotoxicity, NTEP (National Tuberculosis Elimination Programme), Tuberculosis.

INTRODUCTION

Hepatotoxicity, or the harm that chemicals and/or medications do to the liver, is the most important consideration while managing a variety of conditions with chemotherapy and when stopping a medicine once it has been prescribed. Therefore, minimising or preventing hepatotoxicity and comprehending it, are essential for both medical professionals and pharmaceutical companies. Since the liver plays a significant role in the biotransformation of medicines and other foreign chemicals before they can reach their site of action in a harmless state, high sensitivity to medications is noted in the liver. Hepatotoxic drug responses are the most rare and unexpected medication reactions and are influenced by both hereditary and acquired variables.[1]

Both the medications and the subjects have diverse levels of hepatotoxicity, and the severity of the condition varies from moderate, asymptomatic increase of enzymes to progressive, life-threatening liver damage. The only critical needs for the afflicted people are an early diagnosis of the substance causing hepatotoxicity and prompt discontinuation. Since adverse drug responses lack any distinctive characteristics and there is now no good biomarker to detect drug-induced liver damage, adverse drug reactions are typically not detected in their early stages. Hepatotoxicity is similar to liver illness brought on by various aetiologies in terms of biochemistry, morphology, and clinical presentation. In hepatotoxicity individuals, many biochemical tests may also reveal aberrant results akin to liver damage. Abnormal liver tests that show more than twice the upper limit for blood bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) levels are often indicative of liver damage.[2]

In western nations, paracetamol is the most prevalent cause of drug-induced hepatotoxicity. In contrast, anti-tubercular medicines, particularly the INH (isoniazid), are the most common cause of drug-induced liver illness in India. Drug-induced liver illness can present with a variety of clinical signs and symptoms, from asymptomatic abnormalities in liver enzyme levels that often go away with drug withdrawal or continued use to acute hepatitis, a symptomatic condition that frequently leads to fulminant liver failure. The incidence of hepatitis resulting from anti-tubercular medication usage varies between 1% and 36%, depending on the different criteria and drug combinations employed. Alcohol use, advanced age, acetylator status, and the presence of chronic liver disorders have all been linked to an elevated risk for drug-induced hepatotoxicity. The actual mechanism causing this hepatotoxicity is not well known and is still mostly obscure, despite the fact that several causes have been suggested.[3]

Recently, there has been a significant shift in the way TB is treated in India. Standard medications are now administered to patients together with DOTS plus daily therapy. The incidence of hepatotoxicity with this regime has not received much attention in the prior literature. In order to improve compliance with TB treatment, DOTS was adopted; nevertheless, it is still unknown if the DOTS regimen's hepatotoxicity prevalence is different .[4]

In the current investigation, subjects with both extra-pulmonary and pulmonary tuberculosis who were taking anti-tubercular medications were classified as having liver disease if their pre-treatment bilirubin (any) and serum ALT levels were more than thrice as high as the normal range of 0–40 IU/L and >2 mg/dl, respectively.[5] Therefore, the current clinical investigation was carried out to evaluate the incidence of hepatotoxicity in individuals using anti-tubercular

medications as well as the techniques, risk factors, and predictive variables in individuals experiencing hepatotoxicity when using anti-tubercular medications.

MATERIALS AND METHODS

In addition to evaluating the methodologies, risk factors, and predicting variables in individuals developing hepatotoxicity with anti-tubercular medications, the current prospective clinical investigation was carried out to determine the frequency of hepatotoxicity in subjects using these treatments. The study was carried out after obtaining clearance from the concerned Ethical committee. The study population was comprised of the subjects visiting the Department of Respiratory Medicinee of the Institute.

After screening 140 participants, 120 were ultimately added to the trial, since 5 people passed away from hepatic and extrahepatic causes, and 15 subjects did not show up for follow-up. The individuals received DOTS (Directly Observed Treatment, Short-course) treatment in accordance with the NTEP (National Tuberculosis Elimination Programme). Adverse drug responses (ADRs) were identified biochemically and clinically, and the participants were thereafter monitored. All subjects gave their written and verbal informed permission after being fully told about the study's concept.

Subjects with pulmonary or extrapulmonary TB who were treated with DOTS in accordance with NTEP recommended without taking their status into consideration. As well as those who were willing to participate in the study, were the included for the research.

Subjects less than 13 years old, those using drugs that might cause hepatotoxicity, those with alcoholic liver disease, those on modified treatment, those who disregarded DOTS, and those with liver illnesses that were clinically decompensated were all excluded from the research.

In the current investigation, liver disease was defined as serum ALT levels greater than twice the normal range of 0–40 IU/L or both in people with pulmonary and extra-pulmonary TB receiving anti-tubercular medication. Additionally, after stopping the medication, all participants should have improved hepatotoxicity signs and symptoms, and their liver enzyme levels should be within normal ranges. At the study's baseline, 15th, 30th, and 60th days, ALT was measured for each research participant.

If during the first two months of the anti-tubercular medication any subject experienced adverse responses such as oliguria, skin rashes, jaundice, or vomiting, further testing of serum ALT and bilirubin was conducted. 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 were measured in persons exhibiting symptoms of hepatotoxicity.

A liver biopsy was scheduled in a few cases, and medication was maintained in patients with elevated blood ALT or bilirubin levels before biochemical and clinical evaluations. The gathered data were statistically evaluated and reported as a percentage, a number, a mean, and a standard deviation.

RESULTS

In addition to evaluating the methodologies, risk factors, and predicting variables in individuals developing hepatotoxicity with anti-tubercular medications, the current prospective clinical investigation was carried out to determine the frequency of hepatotoxicity in subjects using these treatments. There were 120 participants in this research, both male and female, with pulmonary or extra-pulmonary TB. Table 1 contains a list of the research individuals' demographic details. The bulk of the research participants, 49.16% (n=59), were found to be between the ages of 20 and 39. Following this age range were 28.3% (n=34) for those between the ages of 40 and 59,

13.3% (n=16) for those between the ages of 13 and 19, and 9.16% (n=11) for those between the ages of 60 and 79. In the current study, there were 36.6% (n=44) females and 63.3% (n=76) men. According to Table 1, 50% of the participants (n = 60) had a BMI of less than 18, 43.3% (n = 52) had a BMI of 18–25, and 6.66% (n = 8) had a BMI of 25–29.9.

3.33% (n=4) of the 120 research participants had antituberculosis drug-induced hepatotoxicity (AIH), with 2.5% (n=3) of the men and 0.83% (n=1) of the females experiencing this side effect. 2.5% (n=3) of the participants fell between the ages of 20 and 39, while 0.83% (n=1) of the patients fell between the ages of 40 and 59. According to Table 2, all four research participants experiencing antituberculosis drug-induced hepatotoxicity (AIH) had BMIs less than 18.

After evaluating the clinical characteristics of the research participants, it was observed that 5 study participants experienced nausea (80%; n = 4); 4 study participants experienced vomiting (75%; n = 3); 2 study participants experienced ascites (100%; n = 1); 5 study participants experienced jaundice (80%; n = 4); 1 subject experienced edoema (100%; n = 1); 1 subject experienced encephalopathy (100%; n = 1); and 1 subject experienced coagulopathy (100%; n = 1) had coagulopathy with AIH as shown in Table 3.

DISCUSSION

The current prospective clinical investigation was carried out to evaluate the incidence of hepatotoxicity in patients using anti-tubercular medications as well as the techniques, risk factors, and predictive variables in patients developing hepatotoxicity with anti-tubercular drugs.

There were 120 participants in this research, both male and female, with pulmonary or extra-pulmonary TB. Table 1 contains a list of the research individuals' demographic details. The bulk of the research participants, 49.16% (n=59), were found to be between the ages of 20 and 39. Following this age range were 28.3% (n=34) for those between the ages of 40 and 59, 13.3% (n=16) for those between the ages of 13 and 19, and 9.16% (n=11) for those between the ages of 60 and 79. In the current study, there were 36.6% (n=44) females and 63.3% (n=76) men. Regarding BMI, 43.3% (n=52) of the individuals had a BMI of 18–25, 6.66% (n=8) had a BMI of 25–29.9, and 50% (n=60) of the subjects had a BMI of <18.

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.

3.33% (n=4) of the 120 research participants had antituberculosis drug-induced hepatotoxicity (AIH), with 2.5% (n=3) of the men and 0.83% (n=1) of the females experiencing this side effect. 2.5% (n=3) of the participants fell between the ages of 20 and 39, while 0.83% (n=1) of the patients fell between the ages of 40 and 59. The BMI range for all four research participants experiencing antituberculosis drug-induced hepatotoxicity (AIH) was less than 18. These findings were in line with those of Chowdhury A et al.[7] (2003) and Warmelink I et al.[8] (2011), whose authors found hepatotoxicity parameters that were comparable to those of the authors' current investigation.

For the assessment of the clinical features in the study subjects, one subject had edoema where 100% (n=1) had both encephalopathy and AIH, one subject had encephalopathy where 100% (n=1) had both encephalopathy and AIH, five subjects had jaundice where 80% (n=4) had AIH, four subjects had vomiting where 75% (n=3) had AIH, two subjects had ascites where 100% (n=1) had AIH, and one subject had coagulopathy where all 100% (n=1) had coagulopathy with AIH. These findings were consistent with research conducted in 2017 by Abbara A et al.[9] and in 2016 by Lee CM et al.[10] in which the authors described clinical characteristics in AIH participants that were similar to those in the current study..

CONCLUSION

Within the bounds of its limitations, the current study finds that persons with TB exhibit a low incidence of hepatotoxicity; hence, NTEP and DOTS may be successfully used in tuberculosis subjects without significantly restricting for hepatotoxicity. A few drawbacks of the current study included biases related to geographic areas, a limited sample size, and a short monitoring time. Therefore, further long-term research with bigger sample sizes and longer observation periods will aid in coming to a conclusive result.

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TABLES

Characteristics	Subgroup	Percentage (%)	Number (n)

Age range (years)	13-19	13.3	16
	20-39	49.16	59
	40-59	28.3	34
	60-79	9.16	11
Gender	Males	63.3	76
	Females	36.6	44
BMI (kg/m2)	<18	50	60
	18-25	43.3	52
	25-29.9	6.66	8

Table 1: Demographic characteristics of the study subjects

AIH parameters	Subgroup	Percentage (%)	Number (n)
Gender	Males	2.5	3
	Females	0.83	1
	Total subjects	3.33	4
Age range (years)	13-19	-	-
	20-39	2.5	3
	40-59	0.83	1
	60-79	-	-
BMI (kg/m2)	<18	3.33	4
	18-25	-	-
	25-29.9	-	-

Table 2: AIH characteristics in the study subjects

Variable	Total subjects	Subjects with AIH n (%)
Coagulopathy	1	1 (100)
Encephalopathy	1	1 (100)
Edema	1	1 (100)
Jaundice	5	4 (80)
Ascites	2	1 (100)
Vomiting	4	3 (75)
Nausea	5	4 (80)

Table 3: Clinical features in the study subjects