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Original Article

ANTI TUBERCULAR DRUGS INDUCED HEPATOTOXICITY IN A NEW TERTIARY CARE HOSPITAL OF A TRIBAL DISTRICT OF ODISHA

MANAS RANJAN NAIK[1], MANORANJAN DASH[2], BIBHU PRASAD BEHERA[3*], TRUPTI REKHA SWAIN[4]

[1]Department of Pharmacology, SLN Medical College and Hospital, Koraput, [2]Department of TB and Chest, SCB Medical College and Hospital, Cuttack, [3*]Department of Internal Medicine, SLN Medical College and Hospital, Koraput, [4]Department of Pharmacology, SLN Medical College AND Hospital, Koraput
Email: drbibhu1111@yahoo.com

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ABSTRACT

Objective: India accounts for about one-fourth of the global TB burden. WHO TB statistics for India for 2018 gives an estimated incidence fig. of 2.69 million cases (199 per one lakh population). Drug-induced Hepatotoxicity is responsible for significant morbidity and mortality of the TB patient if these drugs continued after symptoms of hepatotoxicity develop. Whether the hepatotoxicity is due to individual drugs or due to additive effects is still unclear. The management therapy for TB patients with anti-TB DIH is imperative to ensure successful TB treatment and not recurrence DIH. Aim of the current study is to find out the pattern of Liver enzyme raised after antitubercular therapy in the tribal population of Koraput district where different phylogenetic populations reside where clinically it was observed by the physician little early onset of hepatotoxicity than national and international data.

Methods: A prospective study was done after clearance from the Institutional Ethical Committee, Saheed Laxman Nayak Medical College, Koraput, from January 2019 to December 2019. Patients with>15 y of age with pulmonary and extrapulmonary tuberculosis with normal liver enzymes were included. Patients having abnormal liver enzymes before treatment, seropositive TB patients with human immunodeficiency virus infection, pregnant ladies and children<15 y of age were excluded.

Results: Out of 922 patients in total; 4.78% (44) tuberculosis patients developed anti TB DIH. 68.18% (30) patients are below 50 y of age and 31.82% (14) are above 50 y of age group among TB patients with DIH. Age has no statistically significant influence on the occurrence of anti-TB DIH, but there is a statistically significant influence of sex on the occurrence of anti TB DIH. The mean occurrence of anti TB DIH is 18±18.16 d. One case of anti TB DIH patients shows signs and symptoms as early as on day 6th. The commonest symptoms are nausea and vomiting in 64% of patients who developed DIH. Interruption of ATT after DIH occurred in 79.54% of patients with recurrence in only 9.9% of patients after the reintroduction of ATT.

Conclusion: Anti TB DIH mostly occurred between 7-28 d of starting the ATT in this geographical region. The duration of the anti TB ATT regimen is prolonged due to DIH. We recommend that all patients should have LTs 2 w after starting ATT, even if asymptomatic.

Keywords: Tuberculosis, Drug-induced hepatotoxicity, Anti tubercular therapy induced, Drug-induced liver injury

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INTRODUCTION

Tuberculosis (TB) continues to remain as one of the most significant infectious diseases across much of the world. It carries an alarming socioeconomic burden on the individual and society. Tuberculosis remains an important cause of ill health and is one of the top 10 causes of death universally. An estimated 10.0 million with a range of 9.0–11.1 million people fell ill with tuberculosis in 2018 [1]. In 2018, geographically, most tuberculosis cases were in the World Health Organization (WHO) regions of South-East Asia (44%), Africa (24%) and the Western Pacific (18%). India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%), and South Africa (3%) accounted for two-thirds of the universal total [1]. India accounts for about one-fourth of the global TB burden [2]. It is estimated that about 40% of the Indian population is infected with Mycobacterium tuberculosis; the vast majority of those have latent tuberculosis rather than the disease. For 2018, WHO TB statistics for India give an estimated incidence fig. of 2.69 million TB cases (199 per one lakh population) [3]. 50303 and 71131 patients are notified with TB in both the public and private sector in ODISHA in 2018 and 2017 respectively [3].

Revised National Tuberculosis Control Programme (RNTCP) Anti Tubercular Therapy (ATT) is the only cost-effective strategy to treat pulmonary tuberculosis as recommended by WHO. Drug-Induced Hepatotoxicity (DIH) is important and commonly occurring adverse drug reaction (ADR) with Isoniazid, Rifampicin, and Pyraniazide. Due to anti TB drug treatment, the reported incidence of DIH due to anti-TB standards varied between 2.0% and 28.0% depending on population differences and the definition of DIH [4]. A study in India showed that disturbed liver transaminases (33.33%) were common in ADR observed from first-line anti-TB drugs. Nausea and vomiting, hepatitis, rash, headache, constipation, fever, flu-like syndrome, blurred vision and optic neuritis, metabolic disturbances including hyperglycemia, and diarrhea are the other ADRs included [5]. The percentage of patients with single and more than one ADR from first-line anti-TB drugs were 24.09% and 75.9%, respectively, as shown by another study [4]. A higher risk of hepatotoxicity has been reported in Indian patients (6-9) than in their Western counterparts (10-12). The causes for this higher rate of hepatotoxicity in Indian patients are indistinct. Anti TB DIH accounts for 7% of reported drug adverse effects, 2% of jaundice in hospitals, and approximately 30% of fulminant liver failure [13, 14].

Dissimilar suggestions have been made for monitoring liver tests (LTs) in patients on ATT by the American Thoracic Society (ATS) [15], the British Thoracic Society [16], and the European Respiratory Society (ERS) [17] with some favoring a risk factor-based approach. Singanayagam *et al.* compared the two approaches, judging in support of universal testing 2 w into treatment [18].

The Drug-Induced Liver Injury (DILI) Expert Working Group [19] and DILIGEN study [20] use criteria based on ALT, ALP, and bilirubin to guide the stoppage of ATT. All expert recommendations comprise treatment cessation at ALT>5x Upper Limit of Normal (ULN) or if the patient is icteric; ATS recommends cessation if ALT is

3-5xULN and the patient reports symptoms including nausea, anorexia, vomiting, abdominal pain, and jaundice. Each advisory body has recommendations for treatment re-introduction when LTs have normalized; these either opine sequential re-introduction with incremental dose increase or re-introduction at full dosage [15-17].

Anti-tuberculosis drug-induced hepatotoxicity (anti-TB-DIH) may be a consequence of the direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells, and/or liver vasculature [15, 21]. Most types of anti-TB-DIH are attributable to metabolic idiosyncrasy due to the metabolites released or accumulated during the metabolic course. These hypersensitivity or metabolic reactions happen largely independent of the dose [22]. The pathogenesis of DIH caused by Isoniazid is not well understood [23]. Hepatocyte necrosis, ballooning degeneration, and inflammatory infiltrate suggest dose-related toxicity [24]. Whether the hepatotoxicity is due to individual drugs or due to additive effects is still unclear.

DIH diminishes the efficiency of anti-TB management, may lead to non-adherence and can cause treatment failure, recurrence, or drug resistance [25]. DIH is responsible for major morbidity and mortality of tuberculosis patients if these therapies continued after symptoms of hepatotoxicity manifest [26]. The management therapy for TB patients with anti TB DIH is imperative to ensure successful TB treatment and not recurrence DIH.

AIM OF THE STUDY

So the aim of current study is to find out the pattern of Liver enzyme raised after ATT in the tribal population of Koraput district where different phylogenetic populations reside where clinically it was observed by the physician little early onset of hepatotoxicity than national and international data.

MATERIALS AND METHODS

A prospective study was done after clearance from Institutional Ethical Committee, Saheed Laxman Nayak Medical College, Koraput from January 2019 to December 2019. Patients' data were collected from the Department of TB and Chest and Medical Record Department SLNMCH. Patients' demographic data, co-morbidities, addictions, medications, signs and symptoms, details of ATT, time of DIH onset from the start of ATT, duration of withdrawal of ATT, timing of the reintroduction of ATT were collected. Investigations details like sputum for AFB, CBNAAT, Chest X-ray, Urea, Creatinine, Liver enzymes, Serum bilirubin, HIV, Hepatitis, CBC, FBS, HbA1c data also collected for evaluation and analysis. During the beginning of treatment for tuberculosis, those patients who had no abnormal liver functions were taken as study population, and patients with active TB without DIH were considered as control. DIH case was defined as per DILI Expert working Group and DILIGEN CRITERIA.

Monitoring of patients, who started ATT, was done every 7 d by evaluating Liver Function Tests and comparing with baseline values before treatment in those patients who developed symptoms of liver injury. If ATT was more than 3 times Upper Normal Limits with symptoms and 5 times ULN without symptoms, ATT was discontinued. In the case of severe tuberculosis patients, modified ATT regimens were continued. After Liver enzymes come to normal after treatment again ATT started under close supervision and monitoring of liver enzymes by TB and Chest Physician.

Inclusion criteria

- Patients with>15 y of age.
- Those patients with pulmonary and extrapulmonary tuberculosis with normal liver enzymes.

Exclusion criteria

- Patients having abnormal liver enzymes before treatment.
- TB patients with human immunodeficiency virus infection.
- Pregnant ladies and children<15 y of age.

Statistical analysis

The statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 21.0. Discrete variables were presented as frequency and percentages. Continuous variables were presented as means and standard deviation (SD) for unpaired data; a Student t-test was used to compare mean values (for two groups). A Chi-square test was used to determine the significant associations between categorical variables. P-value<0.05* was considered statistically significant and P-value<0.001** was considered statistically very significant.

RESULTS

During the study period, a total of 922 patients were diagnosed with tuberculosis and given ATT in SLNMCH. Out of which 51.41% (474) cases were pulmonary tuberculosis and 46.75% (431) cases were extrapulmonary tuberculosis; the rest 17 cases had no data about the site of the lesion. Out of 922 cases with tuberculosis, we included 44 tuberculosis patients with anti TB DIH (4.78%) in our study that fulfills inclusion and exclusion criteria. They were compared with 44 TB patients without anti TB DIH who were taken as controls.

Table 1: Age distribution

Age	TB patients with DIH (n=44)		TB patients without DIH (n=44)		P-value
	f	%	f	%	
<50 y	30	68.18%	32	72.73%	P = 0.815
>50 y	14	31.82%	12	27.27%	

Table 1 shows in our study population, 68.18% (30) patients are below 50 y of age and 31.82% (14) are above 50 y of age group among TB patients with DIH. Age has no statistically significant (p = 0.815) influence on the occurrence of anti-TB DIH [table 1], but there is statistically significant (p = 0.027)* influence of sex on occurrence of anti TB DILI [table 2]. Table 2 show M: F ratio among TB patients without DIH is 3: 1 whereas it is 1: 1 among TB patients with DIH.

Table 2: Sex distribution

Sex	TB patients with DIH (n=44)		TB patients without DIH (n=44)		P-value
	f	%	f	%	
Male	22	50%	33	75%	P = 0.027*
Female	22	50%	11	25%	

One case of anti TB DIH patients shows signs and symptoms as early as on day 6th and confirmed by lab findings on day 7th; and the last case or delayed case detected on the 42nd day of starting antitubercular drugs. The mean occurrence of anti TB DIH is 18±18.16 d [table 3]. The number of TB patients who developed DIH between 7th to 28th days is more (62%).

Table 3: Time of onset in tuberculosis patients with DIH

Onset of DIH	
Min-max days	6th–42nd day
mean±SD	18±18.16 d

AST, ALT and total bilirubin tests have been conducted in all TB patients with anti-tubercular drugs. Initially, there is no significant difference in AST, ALT, and total bilirubin on day 0.

Table 4: Comparison of laboratory parameters of TB patients with anti TB DIH and without anti TB DIH

Laboratory parameters	TB patients with DIH (n=44)	TB patients without DIH (n=44)	P-value
	In mean+SD	In mean+SD	
Hemoglobin (gm/dl)	10.09±1.32	11.09±1.62	0.002*
Total bilirubin (mg/dl)	1.87±1.25	0.94±0.35	<0.001**
Aspartate aminotransferase/AST(IU/l)	246.97±22.45	40.38±12.37	<0.001**
Alanine aminotransferase/ALT(IU/l)	152.53±11.21	41.64±13.52	<0.001**

Comparison between laboratory parameters of TB patients with anti-TB DIH and without anti TB DIH showed a statistically significant difference. Values are expressed as mean+SD.

Table 4 shows liver function tests conducted for tuberculosis patients at the beginning of diagnosis of DIH. The mean test result for hemoglobin, total bilirubin, AST, and ALT is 10.09±1.32 gm/dl, 1.87±1.25 mg/dl, 246.97±22.45 IU/l, and 152.53±11.21 IU/l, respectively; which are found to be statistically very significant when compared with the same parameters in TB patients without DIH.

Table 5: Impact of anti TB DIH on TB treatment of the patients (N=44)

Impact of anti TB DIH	Number of anti-TB DIH patients (N=44)	
	F	%
Stop all anti-tubercular drugs/interruption of ATT after DIH	35	79.54%
Modified ATT/Substitution therapy (Streptomycin, Levofloxacin, Ethambutol)	8	18.18%
No change in ATT/Treatment continue	1	2.27%
Recurrence anti TB DIH	4	9.09%

After diagnosis of anti-TB DIH, in 35 (79.54%) patients, all anti-tubercular drugs are stopped; in 8 (18.18%) patients, the substitution therapy with Streptomycin, Levofloxacin and Ethambutol (modified ATT) are given after withdrawn of anti-TB therapy [table 5]. In 1 (2.27%) patient; there was no change in anti TB regimen and the treatment with ATT was continued. After treatment with hepatoprotective drugs in those 35 patients in whom ATT was stopped, there was an improvement in liver enzymes and signs and symptoms in all 35 patients after one month. But, in 4 (9.9%) patients, recurrence of anti TB DIH occurs.

DISCUSSION

During the study period, out of 922 patients in total; 51.41% (474) cases were pulmonary tuberculosis and 46.75% (431) cases were extrapulmonary tuberculosis. Out of which, we included 44 tuberculosis patients with anti TB DIH (4.78%) in our study that fulfills inclusion and exclusion criteria. Alu Abbra *et al.* study found the onset of anti TB DIH in 6.9% of tuberculosis patients [27].

Age has no statistically significant ($p>0.05$) influence on the occurrence of anti-TB DIH [table 1], but there is statistically significant ($p<0.05$) influence of sex on the occurrence of anti TB DIH [table 2] in our study. In Gronhagen *et al.* study, female was a risk factor for hepatotoxicity [28]. Maria *et al.* study showed that age and sex not statistically significant influences on the occurrence of anti-TB DIH [29]. With a different result, Buntoro *et al.* study showed that sex did not affect the increase in ALT level but age had an effect on the increase in ALT level in TB patients who were treated with first-line anti-TB drugs [30].

In our study, we found that lower Hb, low body weight and alcohol consumption has a higher rise in liver enzymes. Gronhagen *et al.* study also found high alcohol intake as a risk factor for hepatotoxicity [28].

The commonest symptoms are nausea and vomiting in 64% of patients who developed DIH. Jaundice was found in 28% of the patients who developed DIH. 55% had digestive symptoms and jaundice was the presenting complaint in 10% of patients in the Black *et al.* study [24].

If AST or ALT is more than 5 times the ULN value with or without symptoms and>3 times plus jaundice or hepatitis the ATT should be discontinued [15, 16, and 31]. In our study, anti TB drugs were discontinued in 79.54% of patients as they meet the above-mentioned criteria. In 18.18% of patients, the increase in AST, ALT is not more than 5 times the ULN but in between 2 to 5 times without jaundice or hepatitis. So in these 8 patients, we substitute the recommended ATT with modified ATT Streptomycin, Levofloxacin, and Ethambutol. In one patient (2.27%) there is no significant increase in liver enzymes so ATT is continued but under observation. 9.09% had a recurrence of DIH. These findings were very much similar to Maria *et al.* study, which found interruption in 78.9%, substitution therapy in 15.8%, no change of treatment in 2.27%, and recurrence in 11.4% of anti TB DIH patients [29].

In our study, 62% of anti TB DIH occurred between 7th to 28th days of starting ATT which is quite earlier than other studies. In Alu Abbra *et al.* study, the onset of DIH in 53% of patients was within 2 w [27]. The median time to DIH of 18+18.16 d is comparable with the Singanayagam *et al.* study and Alu Abbra *et al.* study [18, 27] and indicates to us that all patients should have LTs 2 w after starting ATT, even if asymptomatic. The improvement in liver enzymes started from day 10th onwards up to day 25th of withdrawal of ATT and after starting the hepatoprotective drug.

CONCLUSION

Anti TB DIH mostly occurred between 7-28 d of starting the ATT in this geographical region with a median time to DIH of (18+18.16). Maximum patients who developed DIH respond to the hepatoprotective drug with ATT withdrawal of one month. In only 9.9% of patients, there is a recurrence of hepatotoxicity after reintroduction of ATT. The rest of the anti-TB DIH patients completed their anti TB treatment after recovery of one month successfully. But the duration of the anti TB ATT regimen is

prolonged due to DIH. We recommend that all patients should have LTs 2 w after starting ATT, even if asymptomatic.

LIMITATIONS OF THE STUDY

A more extensive study, including large number of patients and for longer period; with an appropriate clinical trial is required to arrive at a firm conclusion.

ETHICAL APPROVAL

The study was approved by Institutional Ethics Committee.

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Nil

AUTHORS CONTRIBUTIONS

All the authors contributed equally in this research work. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

Declared none

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