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Pulmonology

Prevalence of Hepatotoxicity in Patients on Cat-Ⅰ RNTCP Regimen

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Abstract **Original Research Article**

Background: Tuberculosis has emerged as a worldwide health concern with one-third of the world's population being affected by it. The arrival of novel anti-tuberculosis drugs has made it manageable. A number of investigations have been conducted on the issue regarding drug-induced hepatotoxicity; a number of which also include the anti-tubercular drugs, with extensive focus on Pyrazinamide followed by Isoniazid and Rifampicin respectively. None of the studies in this area fully collude with each other, thus, rigorous investigation of both the mechanism of development and risk factors associated with anti-tubercular drug-induced hepatotoxicity need to be conducted. This will help us in gradually getting rid of this deadly disease. ***Objectives*:** To determine the elements that makes a person on anti-tuberculosis treatment more susceptible to develop hepatic toxicity than the others. Analyze the biochemical alterations in such patients. To deduce any correlation and compare the age, sex, history of alcoholism, smoking, nutritional status in patients who develop hepatotoxicity. ***Materials and Methods***: This study was conducted to determine the prevalence of hepatotoxicity in patients on the Cat-I RNTCP regimen in the O.P.D. of the Chest and Tuberculosis Department and RNTCP Centre of Dr. B.R. Ambedkar Memorial Hospital, Raipur, Chhattisgarh. It was a prospective, observational type of study with the aim to deduce the risk factors and biochemical alterations associated with the development of hepatotoxicity. ***Results*:** 4.6% of the patients developed hepatotoxicity during the period of study. Male sex, age greater than 35, malnourishment, poor socioeconomic status and chronic tobacco use were found to be the risk factors associated with the generation of hepatic toxicity. ***Conclusion:*** According to this study, age> 35 years, male sex, chronic tobacco use, malnutrition, and low socioeconomic status are the potential risk factors for the development of hepatotoxicity in patients on the Cat-I RNTCP regimen.

Keywords: Hepatotoxicity, RNTCP, Antitubercular drugs.

INTRODUCTION

Tuberculosis has emerged as a worldwide health concern with one-third of the world's population being affected by it [1]. India alone harbors a fifth (~21%) of the diagnosed patients and is the country with the highest TB burden. According to a report by the World Health Organization, tuberculosis has claimed the lives of 1.4 million people in 2015; the mortality rate in India being 26 per 1,00,000 [2]. The Revised National Tuberculosis Control Program (RNTCP) seeks to implement the WHO-recommended TB control strategy in the Indian scenario. However, despite ambitious measures taken by institutions like the World Health Organization-STOP TB Program, National Institutes of Health of various countries, it still remains a global epidemic. The arrival of novel anti-tuberculosis drugs has made it manageable. But, considering the hepatotoxic potential of the basic drugs- Isoniazid, Rifampicin, and Pyrazinamide- and the exceptional number of people relying on them, it is a matter of great concern if drug-induced liver injury is seen in the chemotherapy of this deadly disease. Anti-TB drugs are known to be one of the commonest group underlying idiosyncratic hepatotoxicity worldwide. The development of hepatotoxicity generates a ripple effect including disruption of treatment, the potential for prolongation of treatment and suboptimal cure. In fact, fulminant hepatotoxicity during treatment has become the major reason leading to the obtrusion of therapy in 11% of the patients [3]. A study has also reported that Indian patients stand at a higher risk [4]. Moreover, anti-TB drug-induced hepatotoxicity has been seen to be associated with a mortality of 6%-12% if the drugs are continued after the onset of symptoms and the risk further increases when the drugs are combined [5].

Despite decades of use and a large number of patients exposed to anti-TB drugs, pathogenesis underlying hepatotoxicity are yet to be clearly understood as none of the studies have gone contradicted. This form of liver injury is a common, but often unrecognized cause of hepatic damage that continues to challenge clinicians worldwide. A study in India [6] found that old age and female sex were more prone to develop anti-tuberculosis drug-induced liver toxicity but this was negated by another study conducted a few years later[7]. Thus, the controversies surrounding this issue and the plethora of inconclusive evidence were the chief reasons behind taking up this study. Studies targeting the identification drug-related, host genetics and environmental factors associated with susceptibility to hepatotoxicity as well as those exploring the potential mechanisms leading to anti-TB drug-related liver injury may allow the development of strategies to reduce the occurrence of hepatotoxicity and its adverse outcome. Since majority of the reported incidences of hepatotoxicity are idiosyncratic, rigorous analysis of host factors might provide some insight as to how this problem can be overcome. This prospective observational investigation tried to analyze the factors which make one person more vulnerable to develop hepatotoxicity than another, both of them being on Cat-I RNTCP regimen. Individual's age, socioeconomic status, addictions, B.M.I (to name a few) were studied and their correlation with development of hepatic damage was drawn. The aim was to unveil any significant pattern which can help us to further improvise the present clinical care policy for the patients taking Cat-I Anti- Tuberculosis treatment. Emphasizing the extent of anti-tuberculosis drug-related hepatic toxicity, this study aims to analyze the prevalence and the predisposing factors in the patients undergoing CAT-I anti-tuberculosis treatment i.e. 2(H3 R3 Z3 E3) 4 (H3 R3) by the Revised National Tuberculosis Control Program in Dr. Bhim Rao Ambedkar Memorial Hospital, Raipur, Chhattisgarh.

MATERIALS & METHODS

This was a prospective observational type of study conducted from mid-August to mid- October in the Chest and Tuberculosis Department and RNTCP clinic of Dr. B. R. Ambedkar Memorial Hospital, Raipur, and Chhattisgarh, India. The study was initiated after the approval of the Institutional Ethics Committee. A number of 112 subjects participated in the study (the proposal stated 20-30 patients but more subjects were included to obtain better results) out of which 1 died and there was a loss of follow up of 4 patients.

INCLUSION CRITERIA

- Patients on Cat-I anti-tuberculosis drugs
- Belonging to the age group 18-60 years
- Should be taking the treatment from Dr. B.R. Ambedkar Memorial Hospital only.

EXCLUSION CRITERIA

- Patients suffering from any hepatic comorbidity before the commencement of treatment. HIV-AIDS patients on Antiretroviral Therapy
- Pregnant and/or lactating females
- If the patient is taking other hepatotoxic drugs
- Pediatric patients

The above-mentioned criteria were set so that strictly the effects of first-line anti-tuberculosis drugs could be observed. The extremes of age were excluded as the hepatic function becomes weaker with increasing age. Patients suffering from HIV/AIDS and other hepatic morbidities, or taking other hepatotoxic drugs were also excluded so that their effects on the liver do not hamper the observations of this study. The site of TB involvement-whether pulmonary or extra-pulmonary, the method of establishing the diagnosis of TB, history of liver disease, history of concomitant use of other hepatotoxic drugs, and alcohol intake and history if previous anti-tuberculosis treatment were recorded. The details of anti-TB drugs (nature of drugs, dosages, duration of treatment, and patient compliance) were noted. The pretreatment liver function test results (serum bilirubin level, AST level, ALT level, and serum albumin level), complete blood count were recorded. Along with these, personal details such as age, sex, height, weight, occupation, and socioeconomic status according to Kuppuswamy scale, addictions; notably history of smoking and alcohol consumption, or any other drugs were recorded. Family history of tuberculosis along with hypertension, diabetes mellitus, and asthma was also noted. On the first visit of the subject, pretreatment values of AST, ALT, serum albumin, serum urea and creatinine, type of tuberculosis and whether the person has tested positive for sputum smear were recorded. The follow-up sessions were held every 2 weeks for a period of two months and the liver function tests, renal function test, complete blood count along with serum albumin were performed again and the values Drug-Induced. The tests were performed in the Clinical Biochemistry and Pathology department of the hospital. Apart from this, the general examination and respiratory examination were also performed upon each visit. Any discomfort experienced by the subject (rashes, itching, abdominal discomfort, loss of appetite, etc.) was noted. The weight of the subject was also recorded upon each visit. The primary endpoint was elevation of hepatic enzyme level to more than 5 times the normal range or AST and ALT levels more than 3 times the upper limit of normal range and patient shows symptoms like itching, nausea, malaise, anorexia, jaundice, etc.

Hepatic damage was confirmed when the following criteria were met:-

I. Total Bilirubin level> 2mg%
II. AST and ALT levels more than 3 times the upper limit of the normal range and the patient shows symptoms like itching, nausea, malaise, anorexia, jaundice, etc.

III. AST and ALT levels more than 5 times the upper limit of normal range but the patient is asymptomatic
IV. Albumin level<3.5mg%.

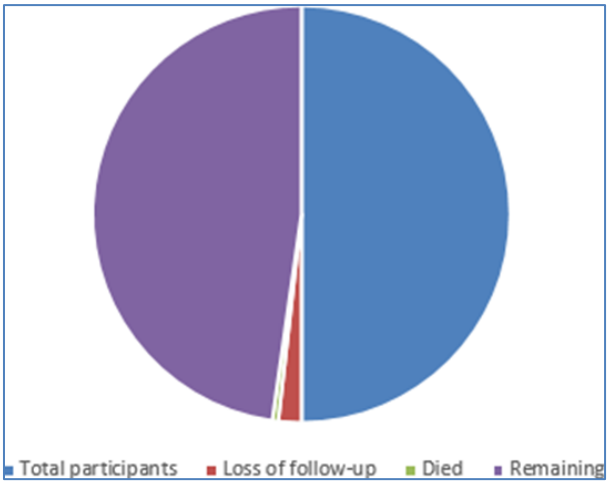
STATISTICAL ANALYSIS

Statistical analysis was done using SPSS, SPSS Inc., Chicago, IL, USA. Data was analyzed by Chi-square ($\chi 2$) test. Data were expressed as "mean (standard deviation; SD)," minimum-maximum and percent (%) where appropriate.

A 'p' value < 0.05 was considered statistically significant. The obtained results were tabulated. The analysis was also done using Student's t-test.

RESULT

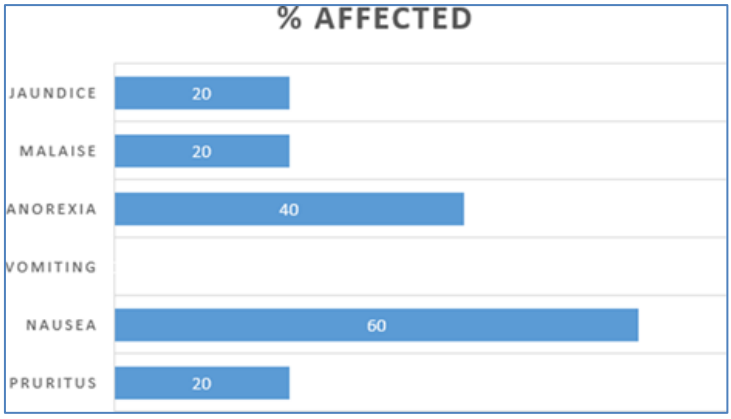
Out of the 112 subjects who participated in the study, 4 failed to follow-up and 1 died during the course of the study. 64.44% were males and 35.56% were females.



Characteristics	Findings
Age(Median)years	36
Male(%)	64.44
Female(%)	35.56
B.M.I(kg/m^2)	22±2.48
Median socioeconomic status(Modified Kuppuswamy scale)	IV

Parameters	Hepatoxicity-yes	Hepatoxicity No	P value
AGE(YEARS)			
<35years	1	67	Fischer exact test = 4.29
>35years	4	35	p value = 0.038
Gender			
Male	4	65	Fischer exact test = 0.551
Female	1	37	p value = 0.458
BMI			
Normal	2	54	Fischer exact test = 0.320
Underweight	3	48	p value = 0.572

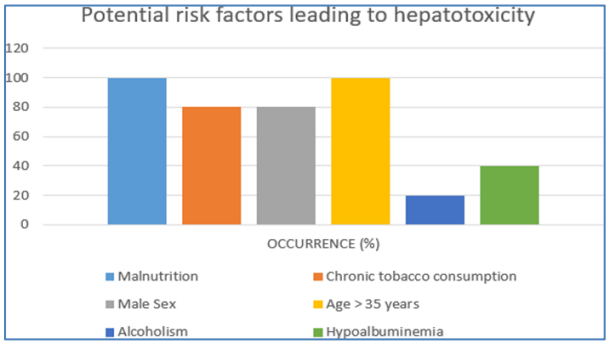
The majority of the patients had pulmonary tuberculosis (61.68%) and out of this 81.82 % were sputum smear-positive. Most of them (66.35%) had been chronic alcoholics at some point in their lives while 63.5% were smokers.4.6% of the subjects- 4 males and 1 female, out of 107 subjects developed anti-tuberculosis drug-induced hepatotoxicity during the study period. None of them were noted to take any other potential hepatotoxic drug during the study period.60% of the affected individuals had Pulmonary Tuberculosis, while 40% had extra-Pulmonary Tuberculosis. The average age was 45± 9.05 years and the average duration of development of hepatic toxicity was 22± 7.26 days. The majority of the patients (80%) who developed drug induced hepatotoxicity were above the age of 40 years, and all of them were above the age of 35 years. Out of the 5, two were borderline malnourished with an average B.M.I of 18.73 kg/m2 while the other 3 were malnourished with an average BMI of 17.3 kg/m2. All 5 patients who developed hepatotoxicity belonged to class IV of the Modified Kuppuswamy scale. 1 of them also had a family history of tuberculosis while 2 had a family history of Diabetes Mellitus. Most of the patients who had developed anti-tuberculosis drug-induced hepatotoxicity also presented the frequently associated signs and symptoms (malaise, anorexia, vomiting, nausea, etc). The most common symptoms being nausea and anorexia (60% and 40%, respectively), followed by malaise and jaundice at 20% each. This has been presented in the graph below:



80% of the patients had been smokers for a period of 18±4.7 years. Compared to this, only 20% had had a history of intermittent alcohol intake for duration of 6 years.1 of the subjects also underwent progressive weight loss during the study period. Along with elevated serum liver enzyme levels, 40% of the patients also presented with moderate hyperbilirubinemia. None of them had abnormal urea or creatinine levels. Hypoalbuminemia was found in 2 patients. Adverse effects involving the gastrointestinal system (40%) and skin (20%) were the other observed symptoms. The various alterations in the biochemical parameters of those who developed hepatotoxicity during the study period have been summarized in the table below:

Parameters	Pretreatment	After 2 weeks	After 4 weeks	After 6 weeks	After 8 weeks
Serum Bilirubin(mg/dl)	0.22±.06	1.02±.044	1.02±.062	0.87±0.26	0.77±.024
AST(IU/L)	29.2±4.78	168±8.76	176±9.81	172±8.40	142±4.47
ALT(IU/L)	27.4±7.43	144±5.44	202±6.74	198.2±6.06	178±4.76
Serum Albumin(g/dl)	3.94±.086	3.12±.012	3.17±0.22	3.24±0.32	3.42±0.57
Hemoglobin(g/dl)	12.86±2.27	12.52±2.33	12.63±1.86	12.69±2.04	12.54±1.56
Serum Urea(mg/dl)	8.72±1.26	7.92±1.38	7.82±1.03	7.74±1.44	8.27±1.62
Serum Creatinine	0.77±0.32	0.76±0.22	0.76±0.24	0.74±0.18	0.84±0.21

Apart from these 5 patients, 18 other patients also showed mild LFT derangement. Their mean AST level was 64±2.6 IU/L and the mean ALT was 72±1.8 IU/L. However, none of them entered the defined criteria for hepatotoxicity during the study period. Thus, the following were found to be the risk factors leading to hepatotoxicity in this study:



DISCUSSION

The incidence of hepatotoxicity during the course of treatment of Tuberculosis has been under study for quite some time. Our study focused on the prevalence of hepatotoxicity in patients undergoing first-line ant tuberculosis treatment of the Cat-I regimen of the Revised National Tuberculosis Control Program in Dr. B. R. Ambedkar Memorial Hospital, Raipur, and found it as 4.6% in the 112 patients who participated in our study. According to our study, age> 35 years, male sex, chronic tobacco use, malnutrition, and low socioeconomic status are the potential risk factors for the development of hepatotoxicity in patients on Cat-I RNTCP regimen. Age greater than 45 was found to be a risk factor in this investigation which is in line with some of the similar studies conducted in this field. Majority of the patients who developed hepatotoxicity were malnourished, i.e. had a BMI<18.5 kg/m2. Hypoalbuminemia was seen in 40% of the patients. An ample number of studies list hypoalbuminemia as a risk factor when it comes to hepatotoxicity development in anti- Tubercular treatment. In another study [10] it was found that patients with hypoalbuminemia had a two-fold higher risk of developing drug induced liver injury. However, the possibility that hypoalbuminemia was caused partly by the development of hepatitis itself is not something that can be overruled. The onset of hepatotoxicity in the current study was 22±7.6 days after the beginning of treatment. This is in line with majority of the studies. Drug induced hepatotoxicity is seen in the first 2 months i.e. during the intensive phase of the treatment.

Anti-tubercular drug-induced hepatotoxicity varies in different countries, ranging from 1% to 10%. In developing countries, it is reported to range from 8% to 10%, while in Western countries it varies from 1% to 3.3% [8]. The variation in the incidence of anti-TB-drug induced hepatotoxicity worldwide may be attributed to the differences in patients' characteristics, indiscriminate use of drugs, and the definition criteria of hepatotoxicity. The relatively higher incidence of hepatotoxicity in the developing countries has been associated with various factors such as older age, higher alcohol intake, malnutrition, intestinal parasitism, past history of jaundice, chronic liver disease, indiscriminate use of drugs, and viral hepatitis, to name a few. Babalik *et al*. [9] have also observed that patients with age >40 years are at higher risk for the development of drug-induced hepatotoxicity, while another study from India [11] has also observed higher prevalence among >60 years of age group.

The higher incidence of Drug Induced Hepatotoxicity in older age may be due to increased prevalence of comorbid conditions as well as use of related additional drugs which are frequently required in this age group. By contrast, a study done in Nepal [12] reported that the incidence of anti-TB-Drug Induced Hepatotoxicity was higher in younger patients. Several studies suggested that female gender is an independent predictor of anti-TB-Drug Induced Hepatotoxicity which is attributed to the variations in pharmacokinetics and slower acetylation status [13]. However, this study showed that males are more susceptible than females to develop hepatotoxicity. Another study by Devarbhavi *et al*. also found greater incidence in males. This could also be due to disparity in demographics and a higher number of men compared to women who participated in this study. As stated by Buchanan and Waltersack *et al*. an adequate intake of nutrients is important for the integrity of liver metabolism and detoxification of TB drugs, as the cytochrome P450 enzyme system is affected by nutrient intake, fasting and malnourished states [14,15]. A recent retrospective observational study by Warmelink *et al*. revealed that a weight loss of 2kg or more developing within 4 weeks during TB treatment is highly significant independent risk factor for drug induced hepatotoxicity [16]. In this study, 20% patients who developed hepatotoxicity lost weight during the treatment but this was not seen in the other 80%. Alcohol can induce enzymes and has potential to cause liver injury. Several studies have demonstrated that alcohol perpetuates anti-TB drug-induced hepatotoxicity. Though this has been established in several studies, there was no such incidence in this study. This could be due to the fact that the patients here were recreational drinkers and did not consume alcohol regularly. The extent of TB disease or the involvement of extrapulmonary organs had no significant association with the incidence of anti-Tb-Drug Induced Hepatotoxicity according to the current study which was in congruence with another study by Yang and Liu in China [17]. However, extrapulmonary organ involvement was reported to be associated with the incidence of anti-Tb-Drug Induced Hepatotoxicity in studies from south India [18]. This difference may be attributed to the fact that extrapulmonary TB may not necessarily indicate severity of the disease. Hepatotoxicity is also seen to be associated with chronic smokers in this study which is in consonance with a study in Brazil by do-Valle [19]. Smoking has been known to cause polymorphisms in the liver enzymes which could show up as hepatic injury. The other presenting signs and symptoms of hepatotoxicity like anorexia, malaise, skin irritation, hyperbilirubinemia, which were observed in some patients are known clinical findings in cases of hepatic injury and have been seen in the majority of investigations conducted in this field. Efforts at prevention and/or early recognition of anti-Tb Drug Induced Hepatotoxicity are severely hampered by limited knowledge of its pathogenesis and risk factors.

Several studies suggest that increasing age is a risk factor for Tb Drug Induced Liver Injury, but often statistical significance was not achieved or hepatotoxicity developed in such cases was not treatment limiting [20]. One study reported a Tb Drug Induced Liver Injury rate ranging from 2 to 8% as age increased, with an average of 5% [21]. Other studies have reported that hepatotoxicity ranges from 22 to 33% in those older than 35 years, compared with 8 to 17% in those younger than 35 years [22]. While this finding has been more or less concordant with this study too, some did not see this as a factor at all.

Future investigations exploring the mechanisms underlying the pathogenesis of anti-Tb Drug Induced Liver Injury should be performed whenever possible so that the novel findings can be translated readily into clinical applications and aid the management of such cases. Intensive study in this field is required to benefit clinicians and patients and hence allow better tailoring of medications based on accurate estimates of risk-benefit ratio. Investigations targeting the identification of environmental, drug-related or host factors responsible for liver toxicity seen in one patient taking the treatment but not in the others will allow us to develop strategies to decrease the adverse outcomes. Since there hasn't been any consensus on these issues, deeper studies are required to answer.

CONCLUSION

According to this study, age> 35 years, male sex, chronic tobacco use, malnutrition, and low socioeconomic status are the potential risk factors for the development of hepatotoxicity in patients on Cat-I RNTCP regimen. Studies like these provide an opportunity for research that will have considerable impact on wide areas such as drug discovery/development process, primary and secondary

care. Undoubtedly, hepatic injury due to a particular treatment reduces patient compliance as well as hampers its course. None of the studies in this area fully collude with each other, thus, rigorous investigation of both the mechanism of development and risk factors associated with anti-tubercular drug-induced hepatotoxicity need to be conducted. This will help us in gradually getting rid of this deadly disease.

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