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Research Article

A PROSPECTIVE STUDY OF ANTITUBERCULOSIS DRUG-INDUCED HEPATOTOXICITY AND ITS MANAGEMENT IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Tuberculosis (TB) is a very common form of droplet infection. If untreated, the disease may be fatal within 5 years in more than half of cases. To study the frequency of anti-tuberculosis therapy (ATT) induced hepatotoxicity was the subject of the present hospital based descriptive study. A higher risk of hepatotoxicity has been reported in Indian patients [3,5] than in their Western counterparts. This prospective study was conducted in the medicine ward of a tertiary care hospital. Patients admitted in the medicine ward with active pulmonary or extra pulmonary TB, who is taking anti-TB drugs regimen were included. Patients were monitored for liver diseases during the hospital and find out the seriousness and management of hepatotoxicity. 91 patients were included in the study. Of the 91 patients, 20 had developed hepatotoxicity. Therefore, the incidence of ADR amounts to be 21.97%. The mean age of patient who has hepatotoxicity is 34.95. Percentage of ADR was more common in patients aged between 21-30 years. The incidences of hepatotoxicity in females and males were 12.8 % and 9.8% respectively. While assessing seriousness, in most of the patients prolongation of hospitalization occurs and in majority of cases management is done by discontinuing the medication. From the study it is concluded that incidence of ADR is higher and females are more prone to get affected with hepatotoxicity. Continues monitoring is needed for the patients with ATT for identifying the hepatotoxicity. Early detection and proper management is needed.

Keywords: Anti Tuberculosis Therapy, Adverse Drug Reaction, Hepatotoxicity

INTRODUCTION

Drug-induced liver toxicity is a common cause of liver injury. It accounts for approximately one-half of the cases of acute liver failure and mimics all forms of acute and chronic liver disease [1]. Although, with the exception of rare cases, drug-induced liver injury subsides after cessation of treatment with the drug, this represents an important diagnostic and therapeutic challenge for physicians. Tuberculosis is becoming an increasingly important problem worldwide, especially with the alarming increase in the incidence of acquired immunodeficiency syndrome (AIDS).' Drug-induced hepatotoxicity is a potentially serious adverse effect of the currently used antituberculosis chemotherapeutic regimens containing isoniazid, rifampicin and pyrazinamide.[2, 4]. The underlying mechanisms of antituberculosis treatment (ATT)-induced hepatotoxicity and the factors predisposing to its development are not clearly understood. A higher risk of hepatotoxicity has been reported in Indian patients[3, 5] than in their Western counterparts [6]. The risk of hepatotoxicity based on data from four prospective Indian studies s greater than 14 published studies from the West. The reasons for this higher rate of hepatotoxicity in Indian patients are unclear. This study is aimed to find out the causality, severity, seriousness, preventability and management of ATT induced hepatitis in tuberculosis patients.

MATERIALS AND METHODS

This prospective study was conducted in the medicine ward of a tertiary care hospital from March to June 2014. Inclusion criteria comprised patients admitted in the medicine ward with active pulmonary or extra pulmonary TB, who are taking anti-TB drugs regimen. Patients having liver diseases before ATT and chronic alcoholics were excluded from the study. Patients were monitored for liver diseases during the admission and follow up were done still discharge. All patient related information was collected in a pre-designed case record form (CRF). The data obtained included demographic details, past history, findings on general and systemic examination, laboratory investigation reports, diagnosis, and treatment. The patients and offending drugs were identified through routine ward rounds by the principal investigators and prescription monitoring of all the departments, and the reports obtained from the health care professionals (nurses, doctors etc). . Management of ADR had been analyzed and categorized as 'Continue with suspected drug', 'Discontinue suspected drug', 'Dose reduced', 'Addition of some other drug' and 'Replacement of suspected drug'. Outcome was be categorized as 'alive with sequalae', 'recovered', 'still under treatment' and 'death'.

Statistical methods

Sample size was estimated at 80 patients.Results are expressed in absolute number and percentages. We have calculated the risk of ADR as number of patients who have developed the event/number of patients at risk of hepatotoxicity. A comparison between incidences of hepatotoxicity in different age groups and gender was performed using Chi-square test. $P < 0.05$ is considered significant.

RESULTS

A total of 95 patients were admitted in the medicine wards with pulmonary or extra pulmonary tuberculosis during study period and 4 patients were excluded as they did not fulfill the inclusion criteria. All 91 patients who fulfilled the inclusion criteria were included in the study and followed up daily. Drug therapy and any changes made in the same were recorded till the patient was discharged. Of the 91

patients, 20 had developed hepatotoxicity. Therefore, the incidence of ADR amounts to be 21.97% in medicine wards. The suspected reactions were recorded in an ADR case report form by a clinical pharmacist for evaluation.

The mean age of patient who have occurred hepatotoxicity is 34.95(Table1). Maximum number of ADR (9/20) occurred in age group of 21-30 years. Total number of patients in this group was 12.When assessed according to their ages we observed that the percentage of ADR was more common in patients aged between 21-30 years which showed 45 % of ADR, while patients between 41-50 years showed 25% and the elderly patients above 60 years showed no ADR. Whereas patients between 50-60 years showed 15% and the occurrence of adverse reactions were observed to be almost similar in patients within the age group of 10-20 years and 31-40 years. The incidences of hepatotoxicity in females and males were 12.8 % and 9.8% respectively (Table 1).

Seriousness criteria assessment showed a frequency 9 (45%) shows prolonged hospitalization whereas 1(5%) of the reactions required intervention to prevent permanent damage and patients who showed adverse reactions with concomitant medical conditions is 10 (50%) (Table 2).

The identified ADRs were reported to the physician for management. The majority of adverse reactions were managed by discontinuing the suspected drug (15.38%) and 6.5% are continued with suspected drug, 6 patients were continued with suspected drug on which 2 were continued by dose reduced and 1 with addition of some other drug. 14 patients were discontinued the suspected drug, on which 7 were discontinued without any other steps and 9 needed replacement of the suspected drug (Table 3).

Table 1: Patient demographics

Variables	Patient with hepatotoxicity (%)	Patient without hepatotoxicity (%)
10-20	10	5.4
21-30	45	15.38
31-40	5	13.18
41-50	25	16.48
51-60	15	24.17
>60	0	26.37
Gender (Male: female)	9.8%:12.2%	53.84%:45.55%

Table 2: Seriousness of hepatotoxicity

Seriousness	Frequency (%)
Life threatening	0
Disability	0
Permanent impairment/damage	5%
Prolonged hospitalization	45
Other medical condition	50%

Table 3: Management of hepatotoxicity

Management	Frequency	Step	N (%)
Continue the suspected drug	6 (6.5%)	Dose reduced Addition of other drugs	2 (2.1%) 1 (1.05%)
Discontinue suspected drug	14 (15.38%)	Discontinue without other step Replacement	7 (7.6%) 9 (9.89%)

DISCUSSION

The use of multidrug regimens for the treatment of TB, such as the combination of INH, RIF, and PZA, has been associated with an increased incidence of hepatotoxicity when compared with INH monotherapy used for anti-TB prophylaxis[7,8]. The incidence of anti-TB-DIH varies worldwide and has been reported to be higher in developing countries where factors such as acute or chronic liver disease, indiscriminate use of drugs, malnutrition, and more advanced TB have been implicated. In our study only 91 patients took ATT during the study period, out of which 20 patients had developed hepatotoxicity. In a study by Hoda A. Makhlouf et.al, 15% of the patients developed anti-TB-DIH, an incidence similar to reports from Asia by Mahmood K, Hussain et.al and Ohno M, Yamaguchi ey.al (8.0–19.8%) [9,10] but this is different from our study where incidence is 21.97% and is higher than those from the West (4.3%) [11].

Several studies reported that females are at increased risk of hepatotoxicity compared with males which is similar to our study where females (12.2%) developed more hepatotoxicity than males (9.8%). However, this difference was not treatment limiting, nor statistically significant [12, 13]. In our study it is found that patients aged between 21 to 30 (45%) are more prone to hepatotoxicity than others but this is different from other study by Sumbal Tariq et.al, were hepato-toxicity is higher in those older than 35 years and females are more commonly affected[15].

The treatment of underlying tuberculosis after the detection of ATT-induced hepatitis is often difficult. A few studies have offered a systematic approach to reintroducing ATT in such a situation [14] though some earlier studies have shown that reintroduction of ATT can be risky[17]. Several regimens have been tried to re-introduce ATT, some starting with isoniazid and others with rifampicin or pyrazinamide. In general, pyrazinamide containing regimens have been found more hepatotoxic[16]. We were able to safely reintroduce isoniazid and rifampicin in most of our patients (96% and 88% respectively) after recovery from hepatitis. In our study out of 20 patients who developed hepatotoxicity, 6 patients continue the Anti-tuberculosis therapy in which 2 patients reduced dose of the drug and one with addition of some other drugs and the remaining 14 patients discontinue the drugs.

In a study by Sumbal Tariq et.al 11 patients had developed hepato-toxicity. Out of 11 patients, three died during treatment, jaundice cleared in remaining 8 patients in 7–15 days, Which is different from our study were only one fatal case is reported , one alive with sequale, fourteen were still under treatment and four recovered before leaving the hospital[15] .

In a study done by Jagdeep Singh *et al* on seventy-two consecutive patients with clinical evidence of ATT-induced hepato-toxicity, jaundice was the presenting symptom in 61% patients; prodromal symptoms were present in 39%, serious complications developed in 16.6% patients, 9 patients died from these complications where as in our study impairment or permanent disability occurs for about 5%, prolonged hospitalization for 45% and other medical condition for 50% of patients[18].

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CONCLUSION

Based on these results, it was concluded that there was a high incidence of hepatotoxicity and females are more prone to get ADR than males. Continues monitoring in the initial 3 weeks may reduce the fatality of hepatotoxicity. In most cases prolongation of the hospital occurs this may increase the burden to the patient and thus there is a chance of discontinuation of treatment. Proper identification of the drug and management is needed for the liver injury as it is reversible in most of the cases after the discontinuation of drug.

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