

## Hepatotoxicity and Hyperuricemia in Patients on Anti Tuberculous Therapy (An Experience at Tertiary Care Teaching Hospital)

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**Abstract:** This descriptive cases series study of six months was conductive to determine the frequency of hepatotoxicity and hyperuricemia in patients on antituberculous therapy at Liaquat University Hospital Hyderabad. Total one hundred and nineteen patients on antituberculous therapy were included in this study. Investigations including liver function tests and serum uric acid level were done. Hepatotoxicity was diagnosed on the basis of abnormal liver function tests. Hyperuricemia there is increase level of uric acid in blood above 7.1mg/dl. (Normal value in male is 2.5-8.0mg/dl and in female 1.5-6.0mg/dl). The average age of the patients was  $48.13 \pm 14.89$  years. Out of 119 patients, 86 (72%) were male and 33 (28%) were female. Frequency of hepatotoxicity and hyperuricemia in patients was observed in 26 (22%) and 15 (13%) cases, respectively. Out of 119 patients 12 (10.1%) had knowledge about the side effect of antituberculous therapy. In conclusion patients treated with INH, Rifampicin and PZA should be closely monitored for initial two weeks and two months of therapy. Rifampicin, INH and PZA should be used in lower therapeutic doses in high risk patients including older and female gender patients.

**Key word:** Tuberculosis • Hepatotoxicity • Hyperuricemia • Rifampicin • INH • PZA

### INTRODUCTION

Tuberculosis is a contagious disease, which spreads as a droplet infection. It is the killer of young adult world wide. Each year 8 millions peoples die from tuberculosis. The largest number of cases occurs in South Asia Region, which accounts for 33% of incident cases globally. Pakistan ranks sixth among the 22 high burden tuberculosis countries worldwide [1].

Tuberculosis is caused by infection with mycobacterium tuberculosis. [2] Drug induced liver injury is a problem of increasing significance. The liver has a central role in drug metabolism and detoxification and is consequently vulnerable to injury. Drug induced liver injury accounts for 7% of reported drug adverse effects, 2% of Jaundice and approximately 30% of Fulminant liver failure [3].

An effective control of tuberculosis has been achieved by the widespread use of antituberculous drugs. There are certain adverse effects ascribed to these drugs. Among these adverse effects hepatotoxicity and hyperuricemia is a well known complication of antituberculous therapy [4].

Antituberculous therapy with Pyrazinamide affects the uric acid and resulting in hyperuricemia [5]. Pyrazinamide is a well known modulator for urate transport via the proximal tubules and it is also an important component of antituberculous therapy. It was reported that among patient's taking PAZ, 51-60% develops hyperuricemia [6]. Therefore considering such scientific facts the present study was focused on hepatotoxic and hyperuricemic effects of antituberculous drugs in patients on tuberculous therapy. The present study builds awareness in patients with tuberculosis and also helps the health care provider as far as management plan is concerned.

### MATERIALS AND METHODS

This descriptive case series study was conducted at Liaquat University Hospital Hyderabad Sindh Pakistan, from January 2009 to June 2009 on patients of tuberculosis who were on antituberculous therapy from one month and maximum three months of duration whereas the exclusion criteria were (a) patient with the presence of serologic evidence of infection with hepatitis

A, B, C, D and E. (b) patient having other metabolic disorders including, Wilson's disease, Hemochromatosis, thyroid disorders, diabetes, pregnancy, carcinoma of liver. (c) Disease with high uric acid level like leukemia, lymphoma, psoriasis or conditions leading to high uric acid level like patients on low dose aspirin or excessive alcohol use. Informed consent was taken from the patients. Detailed history was taken about intake of antituberculous therapy and compliance was evaluated. Investigations including liver function test and serum uric acid level were done. Hepatotoxicity was diagnosed on the basis of abnormal liver function tests. Hepatotoxicity was defined by Alanine aminotransferase more than 2-fold that of upper limit of normal or Alanine aminotransferase / Alkaline phosphate ratio more than 5. Hyperuricemia there is increase level of uric acid in blood above 7.1 mg/dl. The data was collected on the pre-designed proforma. The statistical package for social sciences (SPSS) version 10.0 was used to analyze data. Frequency and percentage were computed for categorical variable like sex, hepatotoxicity and hyperuricemia. Stratification was undertaken for duration of therapy, sex and age of the patients to observe an effect on outcome variables. Mean and standard deviation, 95% confidence interval, median with IQR were computed for quantitative variable age.

## RESULTS

A total of 119 patients who underwent antituberculous therapy from one month to three months duration were included in this study. Most of the patients were from above 45 years of age as presented in Figure 1. The average age of the patients was  $48.13 \pm 14.89$  years (95%CI: 45.43 to 50.84). Similarly average weight and duration of treatment of the patients were  $57.76 \pm 6.27$  kg (95%CI: 56.63 to 58.90),  $2.95 \pm 0.19$  months (95%CI: 2.92 to 2.99).

Out of 119 patients, 86 (72%) were male and 33 (28%) were female. The frequency of hepatotoxicity in patients was observed in 26 (22%) cases whereas the frequency of hyperuricemia in patients was observed in 15 (13%). The rate of hepatotoxicity was high i.e. 36.4% in the 56 to 65 years of age than 28.6% was observed in 18 to 5 years of age, 23.1% was found in 66 to 75 years of age. Similarly rate of hyperuricemia was high i.e. 30% in the 26 to 35 years of age than it was observed in 36 to 45 years of age and 46 to 55 years of age. Regarding gender, rate of hepatotoxicity was higher in female than male (24.4 vs. 15.2%) while rate of hyperuricemia was higher in male patients as presented in Table 1 and 2.

Table 1: Frequency of Hepatotoxicity in relation to gender distribution

Gender	Total	Hepatotoxicity <i>n</i> = 26	Percentage
Male	86	5	15.2%
Female	33	21	24.4%

Table 2: Frequency of Hyperuricemia in relation to gender distribution

Gender	Total	Hyperuricemia <i>n</i> = 15	Percentage
Male	86	15	17.4%
Female	33	0	0%

Table 3: Frequency of Hepatotoxicity in relation to duration of treatment

Duration of Treatments	Total	Hepatotoxicity	Percentage
≤ 2 Months	7	2	66.7%
> 2 months	112	24	21.4%

Table 4: Frequency of Hyperuricemia in relation to Duration of Treatment

Duration of Treatments	Total	Hyperuricemia	Percentage
≤ 2 Months	7	0	0%
> 2 months	112	15	13.4%

Rate of hepatotoxicity and hyperuricemia in patients with respect to duration of treatment are presented in Tables 3 and 4.

## DISCUSSION

Tuberculosis is a global pandemic, with 9 million new cases of tuberculosis disease and approximately 2 million deaths each year, [6] most (98.2%) patients treated for tuberculosis in the United States between 1993 and 2007 had drug-susceptible strains [7].

First line antituberculosis therapy consists of isoniazid, rifampicin, Pyrazinamide, it is thought that isoniazid kill the largest population of mycobacterium tuberculosis, which represents bacilli in long phase growth, after which Pyrazinamide kill the slower-growing population of bacilli in acidic milieu and rifampicin kills non replication bacilli [8].

Drug induced liver injury (DILI) is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies [9].

The predominant forms of DILI include acute hepatitis, cholestasis and a mixed pattern [10].

It is well known that drug induced hepatotoxicity is a potentially serious adverse effect of anti tuberculosis treatment (ATT) containing Isoniazid, Rifampicin and Pyrazinamide [11].

The only measure available for managing ATT induced hepatotoxicity in clinical cases is stopping the offending agents, once there is an evidence of liver damage and reintroducing the same after normalization of liver enzymes [12].

A sample of 119 Patients was selected as per protocol. Out of these cases 86 (72 %) were male and 33 (28%) were female. All patients were on antituberculous drug therapy including INH, Rifampicin and PZA in standard doses as recommended by WHO [13]. According to this study, the frequency of patients who developed clinical & biochemical evidence of ATT induced hepatotoxicity and hyperuricemia in patients was observed in 26 (22%) and 15 (13%) cases, respectively.

In our study, 22% of patients developed ATT induced hepatotoxicity that almost overlaps the study conducted in Japan by Ohno *et al.* [14].

Study by Masood ul haq *et al.* [15] showed that ATT induced hepatitis is 6.95% which do not correlate with the result of our study.

In our study rate of hepatotoxicity was high i.e. 36.4% in the 56 to 65 year of age than 28.6% was observed in 18 to 25 years of age, 23.1% was found in 66 to 75 years age this incidence is correlated to study by Singh *et al.* [16] in this study there is older age groups was affected more as compared to younger one.

Our study has clearly shown that higher incidence of ATT induced hepatotoxicity in females is compared to males (24.4% vs. 15.25) and this result match with previous study by Mahmood *et al.* [4].

Reports by Dorte [17] and Orbrien [18] also supported that ATT induced hepatotoxicity common in females.

Study by Jasmer [19] showed that INH induced hepatotoxicity usually occur in the advanced age (>35 years), in women and in children. Teleman [12] also supported our study that there is higher risk of hepatotoxicity in females.

Vulnerability of females could be due to variation in pharmacokinetics and slow acetylation enzymatic pattern resulting in hepatotoxicity [20].

Advanced age, female sex have been observed to risk factors for the development of DIH. Observations of Sharma *et al.* [21], Bothamly [22], Pande *et al.* [23] and Schaberg [24] also were proved in our study.

Duration of development of hepatotoxicity is variable but early development and deterioration has high mortality as reported by Durand [29]. These facts not correlated with our study; in which hepatotoxicity

occur in 66.7% of patients in less than two months and 21.4% patients develop hepatotoxicity after two months and there is no any mortality recorded.

Observation by Singh *et al.* [16] that site and severity of tuberculosis does not correlate with the severity of ATT induced hepatotoxicity was also proved in this study.

In large Indian study on hepatotoxicity with short course regimens containing rifampicin, isoniazid and Pyrazinamide, there was no indication that Pyrazinamide contribute to the development of DIH [25]. However, in several other studies [26, 27] Pyrazinamide was found to significantly contribute to the development of hepatotoxicity when given along with isoniazid and rifampicin. These studies correlate with our study.

PZA hepatotoxicities appear late, usually two weeks of starting treatment and prognosis is poor [28].

Severe liver injury including death was reported among 5.8% of 1311 subjects treated with rifampicin and pyrazinamide regimen [29], this study not correlates with our study.

In our study, 13% of patients develop hyperuricemia during the course of treatment. Similar finding have been reported in study by Adebisi [30].

Study by Salongi *et al.* [6] showed that the PZA increase the level of uric acid significantly during the course of therapy. Similar finding are reported in Pediatric patients suffering from tuberculosis Significant increase in uric acid mean concentration after one month of therapy of ATT with PZA were observed, which fell again one month after PZA was stopped.

Studies by Sharma and colleagues [31], Zierski and colleagues [32] Khan and colleagues [33] and Inoue and colleagues [34], in which the incidence of hyperuricemia was 43.1, 56.0, 73.7 and 86.3%, respectively in patients treated with combination therapy or PZA alone. These studies support our study but incidence of hyperuricemia is less in our study than these studies. Out of 119 patients in our study 93 cases in our study did not show any evidence of clinical or subclinical hepatotoxicity. Out of 119 patient 104 did not show any evidence of hyperuricemia. This shows that 1st line antitubercular drugs rifampicin, INH and PZA are well tolerated and safe in majority of patients.

## CONCLUSION

This study has shown that, first line antitubercular drugs Rifampicin, INH, PZA are generally safe and well tolerated. There are many side effects of antituberculous

therapy but hepatotoxicity is a definite risk of antituberculosis drugs. The main victims are the high risk patients and those who fail to stop drugs on appearance of symptoms suggestive of hepatitis.

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