ABSTRACT
A prospective study was conducted among 100 patients selected from amongst those who were registered in the Revised national tuberculosis control programme (RNTCP) cell of VIMS Hospital Bellary from January 2012 to the end of June 2012 and they were followed up to December 2012.

The purpose of the study was to evaluate the incidence of drug induced hepatotoxicity (DIH) in proved cases of pulmonary tuberculosis in patients on short term regimen of anti-tuberculosis therapy (ATT) in and around Bellary locality. To study about the predisposing factors for DIH. To study and evaluate the clinical and histopathological features of DIH. Patients above 18 years with sputum positive tuberculosis and patients coming from within and nearby areas of Bellary were included in the study.

Out of 107 patients, 56(52.33%) were males and 51(47.66%) were females. The age group ranged from 20-67 with mean age of 43 years. Out of 95 patients who completed treatment 11 patients had symptomatic rise in serum enzymes with male: female ratio of 1:1.9. Two patients had symptomatic hepatitis with male: female ratio of 1:1. Patients in older age group, malnutrition and cavitary pulmonary tuberculosis disease had symptomatic hepatitis. Needle biopsy of liver confirmed drug induced hepatotoxicity in one patient as the other did not consent for liver biopsy. Re-introduction of drugs done in the patients gradually after serum enzymes reverted back to normal levels. Both patients tolerated well on drug re-challenge. Patients closely monitored and discharged with the advice to get admitted immediately if there are any symptoms of hepatitis.

KEY WORDS: anti tubercular treatment (ATT), drug induced hepatotoxicity (DIH), liver biopsy, liver function tests, subclinical hepatitis

INTRODUCTION:
Tuberculosis remains a world -wide public health problem despite the fact that the causative organism was discovered more than 100 years ago and highly effective drugs and vaccine are available making tuberculosis a preventable and curable disease.[1] India accounts for nearly one fifth of the global burden of tuberculosis. India has more new TB cases annually than any other country in the world. Every year approximately 18 lakh persons develop tuberculosis of which about 8 lakh are new smear positive & highly infectious cases and about 4.17 lakh people die of tuberculosis every year, 2 people die every 3 minutes and a total one thousand person a year.[2] The obstacles to success to include poor patient compliance, drug resistance, insufficient duration, and irregular therapy and last but not the least DIH. DIH is the most unwanted side effect of ATT. Unfortunately almost all the chemotherapeutic agents used in tuberculosis cause hepatotoxicity by single or multiple mechanisms. The absence of overt jaundice, the degree of subclinical hepatotoxicity has to be determined by monitoring the biochemical changes using the liver function tests (LFT). Reports available from studies conducted to assess the hepatotoxicity of Short Course Chemotherapy (SCC) regimens from western as well as many of the Indian studies have shown a high
incidence of hepatitis due to short course chemotherapeutic regimens.

In view of these variable reports on incidence of drug induced hepatotoxicity during SCC, a prospective study was undertaken on 107 patients with pulmonary tuberculosis receiving short course chemotherapy (RNTCP-DOTS). In these patients LFT was monitored for period of 6 months.

**MATERIALS AND METHODS:**

Patients above 18 years with sputum positive tuberculosis and patients coming from within and nearby areas of Bellary were included in the study. Patients who had taken ATT previously or were on ATT at the time of the registration in the RNTCP cell, Sputum smears negative patients, previous history of jaundice, pregnant, those in whom baseline enzyme levels are more than upper limit of normal, patient with diabetes, hypertension and cardiac failure, patients on chronic medication for any other diseases and any pre-existing liver diseases were excluded from the study. The following levels/criteria were consideration exclusion of cases:

1. More than a fivefold ( > 250 IU/L ) elevation of serum enzymes (AST, ALT) or > 150 IU/L on more than 3 occasions and / or
2. Bilirubin > 1.5 mg and / or
3. Clinical features of icteric hepatitis

Patients were given medication on alternate days during the initial phase and for one week during continuation phase. Every effort was made to ensure the compliance of the patient. Minor symptoms were treated symptomatically. Patients with major symptoms were hospitalized. Data collected during these reviews included: Drug taken, any adverse symptoms with reference to liver function.

Liver function tests was done at 1st, 2nd, 4th, 8th, 12th, 16th, 20th and 24th weeks of treatment. Patients who showed the following features are considered significant. Such patients were grouped separately and monitored clinically and bio-chemically every week.

The patients who were irregular in their treatment were grouped separately. Among those who did not take drugs for more than 4 weeks continuously were dropped. Among the 107 patients enrolled in the study, 95 patients were followed up till 24th week. Total number of dropout was 12 patients and none of them had any adverse reactions.

**RESULTS:**

A total of 107 patients were included in the study. In that, 56 (52.33%) were males and 51 (47.66%) were females. The age group ranged from 20-67 with mean age of 43 years. Out of 107 patients, 95 patients were followed up for 24 weeks. The remaining 12 patients, out which 3 patients were followed for 16 weeks, 2 patients for 12 weeks, 4 patients for 8 weeks, 2 patients for 4 weeks and 1 patient was followed for 2 weeks. The total weeks of follow up for all the patients was calculated to be 2394 weeks during this period 13 patients developed drug induced hepatitis (subclinical/clinical) (Table 1).

The subclinical hepatitis which was indicated by elevated serum enzymes was seen in 13 patients and elevated serum bilirubin levels was seen in 5 patients. The clinical hepatitis was seen only 2 patients. The incidence of asymptomatic drug induced hepatitis as reflected by elevated serum enzymes was 12.15% or in other words it was 5.43 per 1000 patient weeks of follow up and similarly the incidence of elevated serum bilirubin levels was 4.67% or 2.09 per 1000 patient weeks of follow up. The incidence of clinical hepatitis was 1.87% or 0.84 per 1000 patient weeks of follow up which is less when compared with the incidence of asymptomatic hepatitis (GRAPH-1).

The incidence of both subclinical and clinical hepatitis was more in the age group of 51 – 60 years when compared with the rest of the age groups. Females had a higher incidence of drug induced hepatitis (both subclinical and clinical) when compared to males (GRAPH-2).

A statistically significant association was seen between age group, sex, type of tubercular lesion and body mass index and incidence of drug induced hepatitis among patients who were on ATT (RNTCP-DOTS) where in patients of higher age group, female sex, cavitatory tubercular lesion and with lower body mass index higher incidence of drug had induced hepatitis (GRAPH-2).

Serum enzymes were elevated in 5 patients in 13 patients. In these only 2 patients developed nausea, vomiting, anorexia, yellowish discoloration of urine and conjunctiva. Increase in serum enzymes are noted as follows: 4 patients on 1st week, 6 patients on 2nd week, and 3 patients on 4th week. Increases in serum bilirubin were noted in 2 patients on 1st week and 2 patients on 2nd week and 1 patient in 4th week. Among the patients who developed jaundice 1 patient was on 1st week and 1 patient on 4th week.
Table 1: Predisposing factors for drug induced hepatitis among patients on ATT (RNTCP-DOTS).

<table>
<thead>
<tr>
<th>Incidence of Drug Induced Hepatitis</th>
<th>Incidence</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 - 30 yrs (n=24)</td>
<td>0.00%</td>
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<td></td>
</tr>
<tr>
<td>31 - 40 yrs (n=28)</td>
<td>3.57%</td>
<td>0.18% - 16.38%</td>
<td>0.00035</td>
</tr>
<tr>
<td>41 - 50 yrs (n=16)</td>
<td>12.50%</td>
<td>2.15% - 35.52%</td>
<td></td>
</tr>
<tr>
<td>51 - 60 yrs (n=18)</td>
<td>55.56%</td>
<td>32.66% - 76.79%</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 yrs (n=9)</td>
<td>0.00%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Male (n=49)</td>
<td>4.08%</td>
<td>0.71% - 13.36%</td>
<td>0.0049</td>
</tr>
<tr>
<td>Female (n=46)</td>
<td>23.91%</td>
<td>13.27% - 37.76%</td>
<td></td>
</tr>
<tr>
<td>Area</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rural (n=32)</td>
<td>18.75%</td>
<td>7.96% - 34.98%</td>
<td>0.3058</td>
</tr>
<tr>
<td>Urban (n=63)</td>
<td>11.11%</td>
<td>4.99% - 20.74%</td>
<td></td>
</tr>
<tr>
<td>Type of lesion</td>
<td></td>
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<td></td>
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<tr>
<td>Cavitative (n=6)</td>
<td>50%</td>
<td>14.66% - 85.34%</td>
<td>0.0319</td>
</tr>
<tr>
<td>Non Cavitative (n=89)</td>
<td>11.24%</td>
<td>5.85% - 19.11%</td>
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<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (n=56)</td>
<td>21.43%</td>
<td>12.16% - 33.59%</td>
<td>0.0285</td>
</tr>
<tr>
<td>Normal (n=37)</td>
<td>2.70%</td>
<td>0.13% - 12.61%</td>
<td></td>
</tr>
<tr>
<td>Overweight (n=2)</td>
<td>0%</td>
<td></td>
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</tr>
</tbody>
</table>

Only clinical and laboratory monitoring was done in asymptomatic patients. In symptomatic patients all drugs were withdrawn and liver biopsy planned, out of 2 symptomatic patients only 1 patient gave consent for biopsy. Biopsy from 52 year male patient showed bridging necrosis and multilobular necrosis. ATT was stopped in both symptomatic patients. LFT returned to baseline in 2 weeks. Then drugs were started as suggested by the British Thoracic Society guidelines. Both patients tolerated the drugs well and continued till the end of treatment period.

DISCUSSION:

In this study of 107 patients of sputum positive pulmonary tuberculosis all were administered category I regimen of RNTCP-DOTS i.e. Isoniazid, Rifampicin, Pyrazinamide and Ethambutol for first two months followed by Isoniazid and Rifampicin for next four months. All were given in thrice weekly basis. Twelve patients dropped out from the study, ninety-five patients were regularly followed till the end of treatment. Out of this, 49 were males and 46 were female patients.

In our study clinical hepatitis occurred in old age patients only (52 years & 63 years). A study from Pande et al\(^6\) also shows that increasing age is associated with more hepatotoxicity. Subclinical hepatotoxicity was noted in eleven patients in age group of 26-61 years. Clinical hepatitis occurred in one male and one female.

Subclinical hepatitis occurred in four male and seven females. Many studies showed female patients are prone\(^3,4\) but in our study there was no difference in clinical hepatitis. This can be explained by small study population and only two patients developed clinical hepatitis. Subclinical hepatotoxicity in our study was more common in females and this is in accordance with many studies.\(^1,3\) Eleven males and sixteen females had mild malnutrition (S. Albumin<3mg). Krishnaswamy says that under nutrition contributes to drug toxicity by various mechanisms.\(^5\) Toxicity and over dosage is
Incidence of drug induced hepatitis among patients on ATT (RNTCP-DOTS)

**Graph 1:** Incidence rate (per 100 patients) of drug induced hepatitis among patients on ATT. ATT- antitubercular treatment.

much more likely to occur with even normal dosage of medicine in the presence of low serum albumin. In our study, both patients who developed clinical hepatitis had mild malnutrition. Subclinical hepatotoxicity developed even in normal individuals.

Advanced disease predisposes to hepatotoxicity. In our study, patients who developed clinical hepatitis had cavitary lesions. Subclinical hepatotoxicity occurred in patients of both cavitary and non-cavitary patients. History of alcohol intake predisposes patients to hepatotoxicity. In our study one patient out of two with clinical hepatitis gives history of alcohol intake. None of the patients were found to be positive for HBsAg or HCV antibody in our study. Hepatitis B virus, Hepatitis C virus patients are more prone to develop drug induced hepatotoxicity. The incidence of hepatotoxicity due to combination chemotherapy has been reported to be from 1% to 39%,[6] 1%[7] and 18%[8] in our study, it was 2.1%.

The frequency of asymptomatic, self-limited elevations of enzymes raises the question of whether the drugs should be stopped when an elevated level is encountered and if so, at what levels they should be stopped. Moreover, the hepatic reactions may develop with such rapidity that even weekly estimations of serum enzymes may not provide sufficient warning. Mild transient and symptom less increase in serum hepatic enzymes are usual during early weeks of treatment whatever the drug regimen and on no account should treatment be interrupted or altered because of these increases. Judgments to withhold or to continue drugs should be based on clinical grounds rather than on laboratory parameters alone in a given case. Increase in serum transaminase activity which occurs later (usually more than one month) has been attributed to pyrazinamide while early increase in serum transaminase (usually <15 days) has been attributed to isoniazid & Rifampicin. Isoniazid toxicity is more common in first few weeks of therapy. In our study both clinical and sub clinical hepatitis occurred in < 4 weeks.

Generally asymptomatic hepatitis is more common than clinical hepatitis. Symptoms are not always reliable but Parthasarathy et al[9] report that
hepatitis is nearly always associated with jaundice. In our study both patients with clinical hepatitis had jaundice and bio-chemical elevation of serum transaminase above 5 folds. Elevation of SAP was also seen in these patients though it was only 2-3 fold raises. S. Bilirubin was raised in 5 patients, but > 4 mg% was seen only in symptomatic patients. After withdrawing the drug all the liver function tests returned to normal level (In 4 weeks in 1 patient and in 2 weeks in another patient). Some workers says patients who developed symptomatic hepatitis does not warrant withdrawing of all the drugs.[10] But since there are a lot of reports of fulminant hepatic failure and death, withdrawal of all the drugs till the elevated serum enzyme level decline to normal level is advisable. In our study, withdrawal of all the drugs was done in both symptomatic patients.

Drug re-introduction is a must, because all are very effective bactericidal drugs. There are 2 schools of thought in drug re-introduction. We followed the guidelines prescribed by the British Thoracic Society.[11] None of the patients developed any reaction on drug re-introduction and the same drugs were prescribed. Patients were discharged with the advice to get admitted immediately if they develop any symptoms of hepatitis which were explained in detail to the patients and their attenders. Both the patients who developed symptoms of hepatitis were screened for Hepatitis A, D, E viruses, Hepatitis B antigen, anti HCV antibody and found to be negative. Since the patients were only on prescribed medications i.e. hepatotoxic anti-tuberculosis drugs, it was concluded that the hepatitis is due to drug toxicity. Liver biopsy specimen correlated with clinical symptoms and bio-chemical test results. Hence drug induced hepatitis was confirmed.
In various studies the dropout ranges from 10 to 40%. In our study drop out was 11.21%. None of them had any adverse reactions.

We cannot predict which patient will develop hepatotoxicity but susceptibility is more in patients of older age group, women, malnutrition and extensive disease states (cavitary PTB). High protein diet, abstinence from alcohol and smoking, good supportive medication with vitamins like vitamin B6, vitamin C will reduce the incidence. Well educated patients and skilled, alert treatment supervisor can reduce hepatotoxicity, fulminant hepatitis and its complications.

CONCLUSIONS:

Asymptomatic rise in serum enzymes was noted in 12.15% of patients and rise in serum bilirubin levels was noted in 4.67% of patients. Even though the incidence of drug induced hepatotoxicity occurred in 1.87% of the patients this is significant. Patients who had clinical signs and symptoms of hepatitis showed typical histopathological changes in the liver. So it is justified to consider liver biopsy in patients with drug induced hepatotoxicity in the presence of clinical symptoms and signs or marked elevation of serum transaminase since it is a simple, reliable and relatively safe procedure. The above findings in our study could be clinically corroborated and also we would like to conclude that the incidence of DIH is more common in patients with malnutrition, old age and advanced pulmonary tuberculosis (cavitary PTB).

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REFERENCES:


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