Study for the Cause of Jaundice in Patients Receiving Anti-Tubercular Treatment

Srivastava B*, Khunjeli R**, Poudyal N***, Khadka S****.

*Senior Consultant and HOD Dept of Respiratory Medicine, **Consultant, Dept of Respiratory Medicine, *** Registrar, Dept of Internal Medicine, **** GDMO, Dept of Respiratory Medicine

ABSTRACT

INTRODUCTION: Many first-line anti-tubercular treatment (ATT) drugs like Isoniazid (INH), Rifampicin (RMP) and Pyrazinamide (PZA) are hepatotoxic. Patients receiving ATT are at the risk for the development of ATT induced hepatitis.

METHODS: Study was conducted between August 2008 to July 2010 at Shree Birendra Hospital, Nepal. All Tuberculer patients on ATT, who developed clinical signs and symptoms of jaundice during the course of therapy, confirmed by deranged LFT, were included. Patients were followed up again at six months.

RESULTS: Tuberculosis was diagnosed among 330 cases in the study period. 17 (5.1%) patients were detected to have jaundice. 13 (76%) patients were detected to have viral hepatitis due to HEV. Only 4 (24%) patients were considered to have true drug induced hepatitis (DIH) due to ATT.

CONCLUSION: Patients who are receiving ATT are at an increased risk for the development of DIH. However, many patients (76% in our study) may have infectious hepatitis. True DIH due to ATT is quite uncommon (1.2% of the total 330 being treated with ATT).

KEY WORDS: Tuberculosis, Hepatitis, Anti-tubercular drug.

INTRODUCTION

Tuberculosis is a fairly common problem in Asia and our country Nepal is no exception. An effective control has been achieved by a very successful DOTS program with a cure rate of 88-90%3. Hepatotoxicity constitutes a major proportion of adverse reactions to ATT2, being reported in 3% of cases treated with Rifampicin (RMP)/Isoniazid (INH) in the USA3, and 4% of cases treated with RMP/INH with or without Pyrazinamide (PZA) in the UK4. Fifteen to 20 percent of patients receiving Isoniazid as a single agent for prophylaxis against tuberculosis may have increased serum alanine (ALT) and aspartate aminotransferase (AST) levels, but only 1 percent have hepatic necrosis severe enough to require the withdrawal of the drug6. A higher risk of hepatotoxicity has been reported in Indian patients3 than in their Western counterparts5. The reasons for this higher rate of hepatotoxicity in Indian patients are unclear although there may be a genetic predisposition7. Reported risk factors for hepatotoxicity include: older age8, female sex9, poor nutritional status10, high alcohol intake, pre-existing liver disease11, hepatitis B carrier state12, increased prevalence of viral hepatitis in developing countries, hypoalbuminaemia and advanced tuberculosis14, and inappropriate use of drugs and acetylator status15,16.

The clinical, biochemical and histopathological features of DIH are indistinguishable from that of viral hepatitis17,18. DIH is normally a rare event; usually a diagnosis of exclusion, in a few susceptible individuals with the risk for a life threatening outcome even in the era of liver transplantation19.

In Nepal we have very few studies about ATT induced hepatotoxicity documented in the literature20,21. In these studies, clinical signs and symptoms of liver disorder, elevation of serum transaminases and jaundice among patients receiving ATT were attributed only to DIH. These patients also had other risk factors for the development of ATT induced hepatitis.
At our center, it was observed that jaundice took a long time to resolve even after discontinuing the ATT. This would not be so if the cause for jaundice was DIH. Despite limited facilities for investigations we decided to do this study to find out the cause for jaundice in these patients and at least to rule out viral and other causes of hepatitis.

**METHODS**

Study was conducted between August 2008 to July 2010 at Shree Birendra Hospital, Nepal. All Tubercular patients on ATT, who developed clinical signs and symptoms of jaundice during the course of therapy, confirmed by deranged LFT, were included in the study. Liver function test (LFT) were done when patients developed jaundice. Hepatotoxicity was defined as increase in serum AST or ALT levels of > 3 times the upper normal limits (UNL) in those with symptoms or > 5 times UNL in those without symptoms. HBsAg for Hepatitis B virus (HBV), IgG and IgM by ELISA immunoassay kits for Hepatitis A virus (HAV), Hepatitis C virus (HCV) & Hepatitis E virus (HEV), were done to exclude viral hepatitis. Patients were followed up again at six months. Patients were excluded if they had any of the following: preexisting acute or chronic liver disease, alcoholism, known patients of hepatitis B or C or concomitantly receiving any known hepatotoxic drugs.

Data analysis was done using chi-square test, t-test and logistic regression with SPSS software program, version 11.5.

**RESULTS**

The study was conducted at Shree Birendra Hospital, Nepal. This is a tertiary care center of the country. A total of 28,951 patients were seen during the study period in the hospital OPDs. Tuberculosis was diagnosed among 330(1.12%) of the total patients. 109(33%) servicemen family patients (68 males and 41 females) were treated from the OPD and 221(67%) serving male patients were admitted in the ward. The study group comprised of young individuals (ranging from 15 – 27 years) with a mean of 22.5 years. 17(5.1%) patients out of the total 330 tuberculosis patients were detected to have hepatitis. 15(88%) were males and 2(12%) were females.

All tuberculosis patients [17(5.1%)] on ATT presented with clinical signs and symptoms of jaundice (Table No 1), confirmed by abnormal LFT. All (100%) patients had nausea, loss of appetite and icterus. 14 (82%) had dark coloured urine, 11 (64%) had loss of weight, 10 (59%) had associated vomiting and 5 (30%) had right upper quadrant abdominal pain. None of the patients complained of pale stools.

**Table 1. Signs And Symptoms**

<table>
<thead>
<tr>
<th>S. N.</th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nausea</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Vomiting</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Loss of Appetite</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Loss of Weight</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Abdominal Discomfort</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Dark Urine</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Pale Stools</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Icterus/ Jaundice</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

The initial Laboratory findings (Table No 2) confirmed that these 17 patients had developed liver cell failure by demonstrating an abnormal LFT. Thirteen patients had positive IgM for HEV. Other virus antibodies e.g. HAV, HBV or HCV were not detected in these patients. Four patients were negative for all the viral markers. These patients were considered to have true DIH due to ATT. Thus true DIH due to ATT was detected to be only 1.2%.

**Table 2 Laboratory Findings**

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEV</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>HBsAg</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>HAV</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>HCV</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

The overall latent period to develop first symptom of jaundice after starting ATT was between 2 to 24 weeks; with a mean of 9.47 and median of 7 weeks in the study group (Table No 2). However, if HEV sero-positives were separated from HEV sero-negatives; two set of patient populations were observed.

13 patients (76%) with HEV sero-positivity were found to develop jaundice later, at any time of ATT exhibition. Their latent period to develop first symptoms of
jaundice was between 2 to 24 weeks with a mean of 11 weeks and a median of 13 weeks.

4 patients (24%) with HEV sero-negativity were detected to develop jaundice earlier, during mainly the intrinsic phase of ATT exhibition. Their latent period to develop first symptoms of jaundice was between 2 to 7 weeks with a mean of 3.7 weeks and a median of 3 weeks.

DISCUSSION

All the patients of this study were young and not having any risk factors for the development of ATT induced hepatitis.

The total percentage of jaundice cases was 5.1% in this study, comparable with many other studies demonstrating similar figures for the development of jaundice in patients on ATT. But 76% of these were due to HEV hepatitis inferring that the true DIH cases were fewer in number i.e. 1.2% only.

A study revealed 8% Jaundice among 50 patients studied and it was more common among the younger individuals. The incredibly high rate of hepatotoxicity could be due to the fact that screening for viral diseases was not done in this study. Another conflicting finding in this study was that hepatitis was commoner among the young population whereas older age group is considered to be a risk factor for the development of DIH in other international studies. Further studies are needed to confirm this finding.

Another study of hepatotoxicity in ATT patients attending the National Tuberculosis Center in Bhaktapur showed that 15% patients developed >51 IU/L increase in AST/ALT among 114 patients. However, the data does not show the age group, how high the ALT was recorded or whether the ATT need to be discontinued due to the hepatotoxicity. A high incidence of viral hepatitis has been reported in TB patients in developing countries, resulting in misdiagnosis of DIH if serologic tests are not performed.

The mean latent period to developing first symptoms of jaundice was of 3.7 weeks among the true DIH patients whereas it was 11 weeks in patients with HEV seropositivity. Thus DIH patients developed jaundice earlier, during mainly the intrinsic phase of ATT exhibition whereas the infectious hepatitis cases developed jaundice comparatively later, at any time of ATT exhibition. This is an important observation seen in this study.

Thirteen (76%) patients diagnosed with infectious hepatitis were all HEV seropositive, indicating that HEV hepatitis is quite common in Kathmandu. Hepatitis due to other viruses e.g. HAV were not detected in this study. There may be a correlation between HEV infection and the development of liver toxicity in patients taking ATT. Further studies are needed to document this hypothesis.

CONCLUSIONS

Patients who are receiving ATT are at an increased risk for the development of DIH. However, many patients (76% in our study) had infectious hepatitis due to HEV infection. We concluded that true DIH cases were fewer in number i.e. 1.2% only, large numbers of patients were found to have other liver pathologies rather than DIH. True DIH patients developed jaundice earlier and resolution was faster as compared with the infectious hepatitis cases.

REFERENCES:

7. Sharma SK, Balamurugan A, Saha PK, Pandey RM and Mehra NK. Evaluation of Clinical and Immunogenetic Risk Factors for the Development of Hepatotoxicity during...


