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Study Of Anti Tubercular Drugs on Liver Function in Newly Diagnosed Pulmonary Tuberculosis Patients

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Abstract: *Tuberculosis is a major health burden in developing countries like India. India accounts for one-fourth of world's TB burden. Annual incidence rate of TB in India is around 2 million and around 300,000 deaths occur due to TB every year. ATT induced hepatitis results in discontinuation of therapy, thereby promoting Mycobacterial resistance. It occasionally is even fatal. When hepatitis due to ATT develops, liver-friendly ATT regimen has to be initiated. But many patients are continued on the modified regimen persistently, even after hepatitis subsides. Here, physicians need to be aware that majority of patients tolerate all the first line drugs on reintroduction. In this context, we undertook a research on establishing the incidence, risk factors for ATT induced hepatitis in reference to the Indian population (South India in particular).* ***Methodology****: This is a prospective study of 100 cases attending to the Department of Pulmonary Medicine in GVP IHC & MT from November 2015 to October 2017.* ***Results and Conclusion****: Incidence of drug induced hepatotoxicity was found to be 3 %. Incidence of asymptomatic rise in serum enzymes was found to be 16 % of patients and incidence of elevated serum bilirubin levels was noted in 9% of patients. These features reverted back to normal before the end of treatment. Patients with age above 35years, female sex and advanced pulmonary tuberculosis (diffuse radiological involvement) were susceptible to drug induced hepatotoxicity. It is essential to monitor the liver function of patients in the initial days of starting ATT as majority were found to develop hepatotoxicity within the first 14 days of initiating ATT.*

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I. Introduction

Tuberculosis is a major health burden in developing countries like India. India accounts for one-fourth of world's TB burden[1]. Annual incidence rate of TB in India is around 2 million and around 300,000 deaths occur due to TB every year[1.] One of the Millennium Development Goals set for 2015 is to reduce incidence, prevalence and death rates associated with Tuberculosis. TB also leads to loss of productivity causing loss of 20-30% of annual household income[2]. Each TB case causes 4.1 DALY (Disability Associated Life Years) of health burden[2]. Anti Tubercular Therapy (ATT) is the cornerstone in the management of Tuberculosis.It is associated with significant side effects, foremost of being hepatitis.

ATT induced hepatitis results in discontinuation of therapy, thereby promoting Mycobacterial resistance. It occasionally is even fatal. When hepatitis due to ATT develops, liver-friendly ATT regimen has to be initiated. But many patients are continued on the modified regimen persistently, even after hepatitis subsides. Here, physicians need to be aware that majority of patients tolerate all the first line drugs on reintroduction. It is important to understand the risk factors for the development of ATT induced hepatitis in a particular population. There is scant literature on this subject in this region.

In this context, we undertook a research on establishing the incidence, risk factors for ATT induced hepatitis in reference to the Indian population (South India in particular).

Aims & Objectives:

- To study the incidence of hepatotoxicity in patients receiving antitubercular treatment.
- To protect the liver from injury by early recognition of adverse effects of drugs used in the chemotherapy
- To know the possible risk factors for the development of drug induced hepatotoxicity.

II. Methodology

This is a prospective study of 100 cases attending to the Department of Pulmonary Medicine in Gayatri Vidya Parishad Medical college & hospital from November 2015 to October 2017.

Inclusion criteria:

Patients newly diagnosed to have pulmonary tuberculosis of age above 18yrs attending OP of Pulmonary medicine were included.

Exclusion criteria:

1. Patients with extrapulmonary tuberculosis.
2. Patients of pulmonary tuberculosis who are relapse, defaulters, treatment failure cases and multidrug resistance cases
3. Patients with abnormal baseline liver function tests.
4. Patients with cirrhosis of liver, acute viral hepatitis and/or gastrointestinal, cardiac diseases.
5. Patients with HIV infection.

TREATMENT

The patients were started on Category I regimen containing Isoniazid, Rifampicin, Pyrazinamide, Ethambutol.

INITIAL PHASE (IP): Isoniazid, Rifampicin, Pyrazinamide & Ethambutol- for 2 months
CONTIUATION PHASE (CP): Isoniazid, Rifampicin- for 4 months

LIVER FUNCTION TESTS:

Patient's liver function was assessed by measuring S.Billirubin, SAP, SGOT, SGPT, S.Proteins, Prothrombin time and GGT. The liver function tests were done prior to drug treatment and then at 2nd**,** 4th, 8th and 24th weeks of treatment.

PROCEDURE: Serum bilirubin, SGOT and SGPT, Alkaline phosphatase and serum proteins were estimated regularly. Competing etiologies particularly acute viral hepatitis, autoimmune hepatitis and other liver diseases are excluded

III. Results

In this study, about 56% of the patients were in the age group of 41 to 60 years, 35% of them were in the 21 to 40 years age group and nearly 9% were over 60 years. The mean age of the study population was 46.56± 13, 55% were males and females constituted 45%.

Incidence of Drug induced Hepatitis

The subclinical hepatitis which is indicated by elevated serum enzymes was seen in 16 patients and elevated serum bilirubin levels in 9 patients. The clinical hepatitis was seen only in 3 patients. The incidence of asymptomatic drug induced hepatitis as reflected by elevated serum enzymes was detected in 16 %. Similarly, the incidence of elevated serum bilirubin levels was 9% and incidence of clinical hepatitis was 3% which is less when compared with the incidence of asymptomatic hepatitis. The incidence of both subclinical and clinical hepatitis was more in the age group of above 60 years when compared to the rest of the age groups. Females had a higher incidence of drug induced hepatitis (both subclinical and clinical) when compared to males.

Predisposing factors for drug induced hepatitis among patients on ATT:

Variables	Count
Age group (in years)	
20-30	13
31-40	22
41-50	23
51-60	33
>60	9
Sex	
Male	55
Female	45
BMI	
Under weight	37
Normal	60

Over weight	3
Radiological distribution	
Localized disease	78
Diffuse disease	22
Albumin levels	
<3mg/dl	61
3-5mg/dl	39
Diabetic status	
Diabetics	24
Non diabetics	76

Statistically significant association was seen between female sex & diffuse radiological disease with the incidence of drug induced hepatitis among patients who were on ATT category 1. Statistically no significant association found between age group, BMI, hypoalbuminemia, diabetic status and incidence of ATT induced hepatitis.

There was no incidence of hepatotoxicity on reintroduction of antitubercular drugs.

IV. Discussion

Hepatotoxicity is a potentially serious adverse effect of ATT. It can cause discontinuation of therapy leading to drug resistance. It is important to understand the risk factors implicated in development of hepatitis, so that the high risk groups can be carefully monitored. Primary care physicians should be aware of the hepatotoxic potential of ATT so that the toxicity can be detected early. Reintroduction is possible in most of the cases.

In the present study, we have recruited 100 patients of tuberculosis diagnosed by either radiological or pathological or by microbiological methods with relevant clinical history and examination. All the patients were put on first line ATT i.e. Isoniazid. Rifampicin, Pyrazinamide and Ethambutol for first 2 months followed by Isoniazid and Rifampicin for next 4 months.

All patients were regularly followed till the end of the treatment without any dropouts. Out of them males were 55 and females were 45 (M:F=1.2:1).

AGE: Advancing age was associated with ATT induced hepatitis in many studies. *In the present study,* majority of patients (56%) were in the age group of 41- 60 years. Mean age in study group was 46.56± 13.0. Clinical hepatitis occurred in 3 patients of age 43, 53, 72 years respectively. Subclinical hepatotoxicity was noted in 16 patients of age group 40-72yrs whose mean age was 51.5± 13.2 There was no statistically significant difference between incidences of ATT induced hepatotoxicity with age distribution of the study group.

Our findings are consistent with studies done by SK Sharma et al[3] and Col Anand et al[4] where *age* was not found to be associated with ATT induced hepatitis. Pande et al[5] showed that increasing age is associated with more hepatotoxicity. Some studies report 4-fold increased risk in patients older than 35 years[6]. In a meta-analysis, Steele et al observed that all age groups are at risk for ATT induced hepatitis. They reported hepatitis in 1 - 6.9% of children compared to 1.6 - 2.5% of adults[7].

SEX: In the present study of 100 patients who were diagnosed with pulmonay tuberculosis, 55 (55%) were males while 45 (45 %) were females. Out of 16 patients who developed sub clinical hepatotoxicity, 11(24.4%) were females while 5 (9%) were males. The difference in gender distribution between the groups was found to be statistically significant (p=0.037). Clinical hepatitis occurs in 1male and 2 female patients (Approx. 1:2). A study done by Pande et al[5] and Devote et al[8] showed ATT induced hepatotoxicity was more common in female patients. Subclinical hepatotoxicity in our study is more common in female patients and this is in accordance with the studies done by Pande and Devote et al [5, 8] . Surendra K Sharma et al[3] in which 51.7% of hepatitis group were females but statistically non-significant. **I**n contrast to our study, a study on North Indian population by Col AC Anand et al[4] did not find female gender to be associated with hepatitis. Dossing et al study showed four times higher risk of treatment limiting hepatotoxicity in women with an overall incidence of 2%[9.]

NUTRITIONAL STATUS: Hypoalbuminemia has been shown to be a surrogate marker for malnutrition. It is linked to increased risk of hepatitis in some studies [3]. Krishnaswamy says that under nutrition contributes to drug toxicity by various mechanisms.[10] In our study, hypoalbuminemia was found in 61% of patients, and all the patients with clinical hepatitis showed serum albumin was less than 3g/dl. Drug metabolism pathways are deranged in states of protein-energy malnutrition, leading to drug induced hepatotoxicity[11.]

DISEASE STATUS: Extensive disease predisposes to hepatotoxicity.

In the present study 36.3% of the patients with diffuse radiological distribution of the disease had subclinical hepatotoxicity. Out of 3 members with clinical hepatitis 2 were having extensive radiological disease with multilobar involvement, one patient had localized disease. ATT induced hepatotoxicity with radiological distribution of the disease is statically significant.

A study done by Pande JN, Singh SPN showed extensive radiological disease was one of the risk factor for ATT induced hepatotoxicity.[5] A similar study done by Devoto FM et al where extensive disease is the risk factor for ATT induced hepatotoxicity.[8]

In the present study diabetics were at higher risk of developing ATT induced hepatitis(p=0.16).There are no previous known studies revealing the risk of ATT induced hepatitis in diabetics. The increased risk could be due to underlying insulin resistance which can lead to excess free fatty acids that are toxic to hepatocytes, thereby causing hepatocyte injury and transaminase elevation[13].It could also be attributed to steatohepatitis and probable disseminated disease which is more common in diabetics. History of alcohol intake predisposes patients to hepatotoxicity. In our study two patients out of three with clinical hepatitis gave history of alcohol intake. None of the patients found to be positive for HIV, HBsAg or HCV antibody in our study. Hepatitis B virus, Hepatitis C virus patients were found to be more prone to develop drug induced hepatotoxicity.[8,5]

COMBINATION OF CHEMOTHERAPY AND HEPATOTOXICITY

The incidence of hepatotoxicity due to combination chemotherapy ranges from 1% to 39%

The following is a list of incidence by some workers

1. Parthasarathy et al [12] - 2-8%, Schberg et al [13] - 11%, Devote et al [8] - 9.9%, Steele et al[7] - 2.6%, Dossing et al [9] - 8%, Kamat et al from Bombay [14] - 18%, Sivaraman et al [15] - 7%. In the present study it is 3%

The Tuberculosis Research centre, Chennai (1983) has published first report on short course chemotherapy (SCC) on South Indian patients.[16]

All patients in this study received INH and Pyrazinamide and 2/3rd of them also received Rifampicin. Hepatitis occurred in 17 (2.5%) of the 693 patients. In addition 14(2%) had transient elevation of aminotransferases detected during routine monitoring. It was noted that eight patients who developed hepatitis during first two months were from Rifampicin series

V. Conclusion

1. Incidence of drug induced hepatotoxicity was found to be 3 %.
2. Incidence of asymptomatic rise in serum enzymes was found to be 16 % of patients and incidence of elevated serum bilirubin levels was noted in 9% of patients. These features reverted back to normal before the end of treatment.
3. Patients with age above 35years, female sex, and advanced pulmonary tuberculosis (diffuse radiological involvement) were susceptible to drug induced hepatotoxicity
4. It is essential to monitor the liver function of patients in the initial days of starting ATT as majority were found to develop hepatotoxicity within the first 14 days of initiating ATT.

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