Original Article

Level of hepatic enzymes and serum zinc and copper at start of Anti-tubercular treatment (ATT) and a onset of hepatitis induced by ATT

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ABSTRACT

Background: *Hepatitis is common adverse effect seen after starting anti tubercular treatment. Anti-tubercular drugs namely. Isoniazid, Rifampicin and Pyrazinamide are potentially Hepatotoxicity drugs. These drugs are metabolized by the liver. No Hepatotoxicity has been reported for Ethambutol or Streptomycin.*
Objectives: *The present study was performed to see the changes in serum levels of hepatic enzymes (SGOT. SGPT& ALT Phosphatase) & serum Bilirubin & Copper (Cu), zinc (Zn) microelements in tuberculosis patients having Hepatotoxicity after anti tuberculoid treatment (ATT).* ***Methods:*** *It was an a prospective longitudinal study. A total of 685 tuberculosis patients was included in study. Patients were treated with Isoniazid (H) 300mg, Rifampicin(R) 450mg. Pyrazinamide(Z) 1500mg Ethambutol (E) 1000mg for two months followed by IN14-300mg. Rifampicin 450mg for next four months. Serum levels of hepatic enzymes (SGOT, SGPT& ALT Phosphatase) & serum Bilirubin & Copper (Cu), zinc (Zn) microelements was estimated at start of ATT and after onset of hepatitis.*
Results: *Out of 685 patients, 46 patients developed Jaundice with Hepatomegaly within six weeks of treatment. SGOT, SGPT, serum Bilirubin & copper were increased significantly ($p<0.05$). Antitubercular drugs were withdrawn at the onset of jaundice. The level of serum zine declined significantly after hepatitis ($p<0.05$).*
Conclusion: *Serum SGOT. SGPT. Copper levels were increased at the onset of hepatitis when compared with the levels which obtained before start of ATT & zinc levels decreased after ATT. There was no significant changes found in serum levels of alkaline phosphatises.*

Keywords: *Hepatitis ATT, Zinc. Copper, Liver Function Tests.*

How to cite this article: Kumar A, Singh M, Singhal KC, Bansal AK. Level of hepatic enzymes and serum zinc and copper at start of Anti-tubercular treatment (ATT) and a onset of hepatitis induced by ATT. J Pharmacovig Drug Safety 2023;20(1):6-9.

Source of Support: Nil, **Conflict of Interest:** None

Received:20.12.22
Accepted:14.01.23

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INTRODUCTION

Tuberculosis is a persistent inflammatory illness characterised by the formation of granulomas, and it poses a significant health challenge in poor nations. Tuberculosis, despite the existence of medicines, continues to be a prominent cause of mortality on a global scale.[1]

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DOI: 10.21276/jpds.2023.20.01.02	

The updated assessment in the most recent 2014 global tuberculosis report by the World Health Organisation indicates that there was an increase of about 500,000 tuberculosis cases worldwide in comparison to the reports from 2013. According to the estimation by the World Health Organisation (WHO), around 9 million individuals worldwide contract active tuberculosis each year, resulting in 1.7 million deaths annually.

Approximately 2 million individuals in India get active disease annually, resulting in approximately 0.5 million

fatalities. The reported incidence of anti-TB-associated Hepatotoxicity ranges from 2% to 28%, depending on the diagnosis criteria and population being studied.[2]

The U.S. Food and Drug Administration (FDA) has approved 10 medications for the treatment of tuberculosis.[3] Among these four medications, three are frequently utilised due to their notable antitubercular effectiveness and minimal toxicity. These treatments are referred to as first-line anti-tuberculoid medications.

- Isoniazid (H)
- Rifampicin (R)
- Ethambutol (E)
- Pyrazinamide (Z)

These four drugs are prescribed Initial two months of treatment which is called as extensive period, followed by continuation period in which drugs are reduced to two which continues for 4-8 months depending upon condition of patients.[3]

These drugs have either low antitubercular efficacy or high toxicity or both, are used in special circumstances only.

From the absence of symptoms and an increase in liver enzymes in the blood to severe liver damage that necessitates a liver transplant. Genetic diversity influences the rate of INII acetylation. The following options are available: Fast acetylators, which make up around 30-40% of Indians, have a half-life (t1/2) of 1 hour for INI.

Approximately 60-70% of Indians are classified as slow acetylators, meaning that the half-life of isoniazid (INH) is 3 hours for this population.

Peripheral neuritis caused by isoniazid seems to be more prevalent in individuals with delayed acetylation.

Prophylactic administration of pyridoxine (10mg) effectively avoids neurotoxicity, even when greater doses are used. However, regular use is not obligatory. Pyridoxine 100mg/day is used to treat INH neurotoxicity.[4]

Hepatotoxicity is a significant negative consequence of INH. It is infrequent in youngsters, but more prevalent in older individuals and those who abuse alcohol. Acetyl hydrazine, the metabolite of INH, induces liver damage in adults, making hepatic damage more prevalent in Fast-Acetylators.[5]

Rifampicin: the occurrence of negative effects is comparable to INH. Hepatitis is a significant negative consequence that typically arises in individuals who already have liver illness, and its occurrence is directly proportional to the dosage of the treatment. If jaundice develops, it is necessary to stop taking the medication. The death rate linked to Anti-Tuberculosis treatment has been documented at 16 cases out of 500,000 patients who were administered RIF.[6]

Pyrazinamide: Hepatitis is the most significant side effect associated with dosage, although it seems to occur less frequently in the Indian population compared to Western countries. The current recommended daily dosage is restricted to 25-30mg/kg, resulting in a minimal occurrence of Hepatotoxicity.

Ethambutol is a medication. Ethambutol (ETH) is a semi-synthetic antibiotic that is exclusively used in conjunction with other medicines like INH and RIF. A small number of people taking ETH have experienced infrequent instances of acute and symptomatic liver damage. The most significant toxicity associated with optic neuritis is the impairment of visual acuity and colour vision, which depends on the dose and duration of therapy.[4]

Streptomycin is a medication that is capable of killing tuberculosis bacteria. However, it is not as efficient as INH or rifampicin. It is known to cause damage to the ears and kidneys, a condition known as ototoxicity and nephrotoxicity, respectively. The usage of streptomycin has decreased because it requires injections into the muscles and has a narrower safety margin. Serum zinc and copper trace elements change in the presence of Hepatotoxicity.

METHODS

This prospective longitudinal study was done in J.N medical college, AMU, Aligarh, UP. A total of 685 patients were taken on short-term chemotherapy for pulmonary tuberculosis. Ethical approval and prior permission was obtained from institutional ethical committee before commencement of study

Source of patient

The patients attending the chest outpatient department (OPD) were enrolled in to the present study

Inclusion criteria

Patients included in the study were 15-64 years of age (mean 44.5years) suffering from tuberculosis. Out of them 422 are males and 263 are females.

Exclusion criteria

Pre-existing hepatic or renal diseases, Alcoholics, Pregnant women.

Patients were treated daily for 2 months with 300mg- H+ 450mg –R+1500mg-Z+1000mg ethambutol Followed by for 4 months with 300mg-H+ 450mg-R.

Investigations

Liver function tests (LFTs): SGOT, SGPT. Alkaline Phosphatase. Serum Bilirubin were determined by using kit methods in Biochemistry lab. J.N. Medical College.

Estimation of serum Zine(Zn) and copper (Cu) levels was done by GBC 902-double beam atomic absorption spectrophotometer The followed method is a standard method developed in 1955 by Walsh and as quoted by Kryska et al.[8]

STATISTICAL-ANALYSIS

The data was expressed as mean +S.E.M. Data entry was done using Microsoft excel sheet and statistically analyzed (SPSS 20.0) by using student's' test to compare the data obtained during hepatitis and at recovery. Value of $P<0.05$ were considered statistically significant.

RESULTS

46 patients out of 685 patients developed jaundice with anorexia, nausea vomiting, fever and hepatomegaly within six weeks after starting treatment. Incidence of jaundice was higher in males ($p<0.001$) with poor nutritional status.

Antitubercular treatment was withdrawn at onset of jaundice. Only 2 out of all patients could not recover from jaundice and died. Hepatitis was observed in both male and female patients nearly to equal extent.

In this study, Hepatocellular (group-B) as well as Cholestatic (group-A) hepatitis was suggested by L.FT. Were seen during ATT former being apparently more common. In both the groups transaminases (SGOT, SGPT) were markedly increased at the onset of hepatitis: The values of SGOT, SGPT at the onset of hepatitis were 99.04 +2.07 and 101.38+3.380 respectively, which were significantly higher than the values obtained at start of ATT, which were 15.35+0.96 and 13.11+0.78 respectively ($p<0.05$). Serum alkaline Phosphatase values did not changed much whereas changes observed in serum Bilirubin levels were statistically significant(<0.001). The results of LFT estimations are summarised in (Table 1). The levels of microelements were also found to be altered during ATT induced hepatitis. Serum Zn levels were significantly ($p=0.05$) decreased at the onset of hepatitis in both the groups when compared with the values obtained at start of ATT. The serum Cu levels were significantly increased in both the groups of hepatitis (Table-2).

The level of serum zinc significantly ($p<0.05$) declined to 94.20+3.06& 144.42+2.53 in both group-A (Cholestatic hepatitis) & group-B: (Hepatocellular hepatitis) respectively when compared with values obtained at start of ATT & which were 140.31-1.91 (group-A) and 166.81+2.68 (group-B) respectively (Table-2). Serum copper was raised to 167.57+2.05 & 200.97+3.03 in both Group-A and group-B respectively as compared with earlier values of group-A was 139.68+2.11 and Group-B was 162.78+1.99 (Table-2).

Table 1: Liver function tests in tuberculosis patients before and onset of ATT induced Hepatitis

Liver Function Tests	At Start of ATT	At Onset of Hepatitis	P-Value
SGOT (IU/L)	15.35+0.96	99.04+2.07*	p<0.05
SGPT(IU/L)	13.11+0.78	101.38+3.38	P<0.001
Alkaline	10.65+2.14	17.76+0.46	p>0.05
Phosphatase			
(KAU/100ml			
Serum bilirubin (mg	0.59+0.03	2.00+0.22**	P<0.001
%			

n=46.

The values are meant+ S.E.M

*p<0.05** As compared with respective values obtained at start of ATT.

Table 2: Scrum levels of copper and zinc in tuberculosis patients before and onset of ATT Induced hepatitis.

Trace elements	Group A (n=20) Cholestatic Hepatitis	Group B (n=26) Hepatocellular Hepatitis			p-value
	At start of ATT	At onset of hepatitis	At start of ATT	At onset of hepatitis	
Zn(ug/dl)	140.31+1.91	94.20+3.06**	166.81+2.68	144.42+2.53**	P<0.001
Cu(ug/dl)	139.68+2.11	167.57+2.05**	162.78+1.99	200.97+3.03**	P<0.001

The values are mean +S.E.M

*p<0.05 As compared with respective values obtained at start of ATT.

DISCUSSION

An assessment was conducted to determine the frequency of liver injury resulting in jaundice among 685 patients undergoing short-term chemotherapy for pulmonary tuberculosis. The hepatotoxic effects of anti-TB medications typically manifest within the initial 2 months of treatment, although they can occur at any point during the treatment duration. Hepatotoxicity, a severe adverse pharmacological reaction observed in tuberculosis (TB) patients undergoing treatment with anti-TB medications, is a significant and complex clinical issue of global concern. Tuberculosis (B) continues to be a significant infectious disease and a leading cause of disability and mortality globally, despite notable socioeconomic progress and advancements in medical sciences.[9]

Despite the growing recognition among healthcare professionals and the general public, this issue continues to pose significant challenges and is responsible for hospital admissions and life-threatening incidents. Roughly. It is estimated that around one third of the global population is afflicted with tuberculosis.[10]

Among the several detrimental consequences of anti-TB medications. Hepatotoxicity is a severe and crucial issue that affects both patients and clinicians. The interaction between regulatory bodies and drug developers can result in treatment disruptions, the development of drug resistance, severe liver harm, and potentially even death in patients with tuberculosis.[11]

Hepatotoxicity is a severe and undesirable complication of anti-TB therapy, encompassing a spectrum of effects from asymptomatic increase in liver enzymes in the blood to sudden liver failure.[12]

The occurrence of INH-associated hepatitis was 6%, while the occurrence of hepatotoxicity with the combination of INH and RIF was 30%, suggesting that the combination treatment significantly increases the occurrence of hepatotoxicity.[13]

In general, the occurrence of liver damage caused by anti-TB treatments has been documented in 5%-28% of patients undergoing treatment with these medications.[14] The prevalence of anti-TB-DIII in the Indian population was 14.3%.[15]

INH is a highly effective inhibitor of various types of cytochrome P450, such as CYP1A2, 2A6, 2C19, and 3A4. Of all the cytochromes, CYP1A2 is particularly important in the process of detoxifying hydrazine. Consequently. INH is the primary culprit for inducing its own toxicity, potentially through the inhibition of these enzymes.[16,17]

The aetiology of Hepatotoxicity remains elusive and is typically infrequent in those under the age of 20. Acetylhydrazine, the metabolite of INH, induces liver damage in adults, making hepatotoxicity more probable in individuals who metabolise it rapidly. Alcohol consumption and pre-existing liver illness are other factors that contribute to hepatotoxicity. Typically, hepatotoxicity arises after initiating INII medication.[5]

Patients with normal hepatic function typically do not experience liver damage, even when both INII and rifampicin are administered. Nevertheless, deadly hepatitis can occur, especially in individuals who consume alcohol, have pre-existing liver impairment, are elderly, or are using other severe hepatotoxic drugs concurrently. These factors enhance the likelihood of hepatotoxicity.[5]

Pyrazinamide is detected at a dosage exceeding 40mg/kg per day. Jaundice frequently serves as the initial sign. Elevated levels of Alanine and Aspartate aminotransferase are detected upon investigation. A daily dosage of less than 30 mg/kg is unlikely to cause liver damage. Administration of antitubercular medication, whether using Isoniazid, rifampicin, or Pyrazinamide alone or in combination, increases the likelihood of liver impairment in patients.[18]

Before administering Pyrazinamide, all patients should undergo a liver function test. Pyrazinamide should not be provided if there are any indications of liver illness.[3]

Bhandari S et al. observed a considerable increase in the average serum zinc concentration in patients following the end of DOTS therapy (P<0.001). A study conducted by Hassan Ghulam et al. found that the average serum zinc content in individuals with pulmonary tuberculosis before treatment was significantly low.[20] In his study, Ray et al. confirmed that serum zinc levels decreased in 50 children with tuberculosis during a period of 6 months of antitubercular medication, in comparison to 10 healthy children and 10 malnourished children without tuberculosis.[21].

The decreased serum zinc levels in individuals with tuberculosis (TB) may have multiple contributing factors. A separate study revealed a notable decrease in serum zinc levels in tuberculosis patients in comparison to control patients, although copper levels were elevated.[22]

Insufficient levels of zinc and selenium can heighten the likelihood of contracting tuberculosis and make persons more susceptible to oxidative stress. Copper has a role in the innate defensive mechanism against reactive oxygen species.23 Measuring serum copper levels can be a crucial factor in assessing the continued presence of non-conversion after one month of tuberculosis treatment.[24]

In our study, level of serum zinc declined to 94.20+3.06 & 144.42+2.53 in both Group-A and Group-B respectively& serum copper raised to 167.57+2.05 & 200.97+3.03 in both groups of patients who developed hepatitis (Group-A and Group-B). Accumulation of copper has been associated with damage to liver, in the context of previous observations the generalization,[25, 20,27,28,29] that in hepatitis. serum copper levels increase and serum zinc levels decrease is justified by the results obtained in the present study, however the difference that hepatitis as confirmed by serum enzyme and Bilirubin levels in the present study was drug induced, made no difference in the serum level changes of microelements.

CONCLUSION

Hepatitis was observed in both males and female patients nearly to equal extent. After 6 weeks of treatment serum SGOT, SGPT and Bilirubin levels was increased significantly & alkaline Phosphatase was also raised but not statically significantly. Serum Zn levels was decreased & Cu level was increased significantly in both Cholestatic and Hepatocellular hepatitis:

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