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Frequency of anti-tuberculous therapy-induced hepatotoxicity in patients and their outcome

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Abstract

Background: Tuberculosis (TB) is a very common droplet infection especially in the northern areas. If untreated, the disease may be fatal within 5 years in more than half of cases. To study the frequency of anti-tuberculous therapy (ATT) induced hepato-toxicity was the subject of the present hospital based descriptive study. Method: The study was conducted in Medical Unit, Ayub Teaching Hospital and patients with diagnosed Tuberculosis in whom ATT was initiated were included in the study. The subsequent development of elevated liver enzyme levels and hepatitis, amongst some members of the study group; was diagnosed, with the help of clinical findings and Liver Function Tests (LFT's) and were dealt with according to severity. Results: Out of the 500 patients studied 277 (55.4%) were male and 223 (44.6%) were female, 203 (40.5%) were in age group 21-35 years, 136 (27.1%) in age group 36-50 years, 141 (28.1%) in age group 51-65 years while 20 (4%) were above 65 years of age. Out of them 40 (8%) developed hepatotoxicity, 21 (4.2%) patients amongst the study group developed overt hepatitis, 20 (4%) of them made an uneventful recovery while 1 (0.2%) died of Fulminant Hepatic Failure (FHF). Conclusions: ATT-induced hepato-toxicity, was frequently encountered in patients put on ATT.

Keywords: Tuberculosis (TB), Anti-Tuberculous Therapy (ATT), Fulminant Hepatic Failure (FHF), Multi Drug Resistant (MDR), Liver Function Tests (LFT's).

Introduction

Tuberculosis (TB), is a very common droplet infection, especially in northern Pakistan. To study frequency of ATT-induced hepato-toxicity was the subject of the present hospital based descriptive study at Ayub Teaching Hospital, Abbottabad.

With effective, timely, and proper chemotherapy, patients have a very high chance of being cured. However, improper use of anti-tuberculosis drugs, while reducing mortality, may result in large number of chronic infectious cases, often with drug resistant bacilli. Therefore it is necessary to treat Tuberculosis promptly and effectively.

INH is regarded as a most useful drug in TB. It is metabolised primarily by Acetylation to Acetyl Isoniazid, mainly in the liver. Metabolic activation of liberated hydrazine produces a chemically active acylating agent, which is responsible for hepatic damage. Patients who are Rapid Acetylators of INH are at greater risk of developing hepatotoxity. The response rate is variable and hepato-toxicity can occur within a week or up to one year later, though most cases occur during the first 1-2 months.[1,2] Severe and fatal hepatitis has been reported with INH therapy. The risk of developing hepato-toxicity is age related; with an incidence of 8 cases per 1,000 persons older than 65 years. It is rare in patients under 20 years of age. In addition, the risk of hepatotoxicity is increased with daily consumption of alcohol. Mild hepato-toxicity, as evidenced by a transient elevation of serum transaminase levels occurs in 10-20% of patients taking INH. This abnormality usually appears in the first 3 months of treatment, but it may occur anytime during therapy. In most instances, enzyme levels return to the reference range, with no need to discontinue the medication.[3,4]

Occasionally, progressive liver damage can occur. Most reactions of minimal-to-moderate severity are followed by recovery and no significant fibrosis. Submassive hepatocellular injury may be followed by fibrosis, nodular regeneration, bridging and multilobular necrosis and cirrhosis. If hepato-toxicity occurs with INH as evidenced by Aminotransferase levels more than 5 times normal or clinical hepatitis continuation of the drug can lead to Fulminant Hepatic Failure and death; so INH should be discontinued at once.[4,5]

Rifampicin another very useful drug can also cause hepatitis. This especially occurs in the elderly, alcoholics or patients of Chronic Lung Disease (CLD). It induces liver enzymes and thus transiently raises their levels. Rifampicin should be stopped if the Serum Bilirubin becomes elevated or if the transferases are more than three times elevated.[6]

Pyrazinamide can also cause hepato-toxicity although it is rare with the recommended doses used nowadays. However, it can cause hepatic necrosis in doses of more than 40 mg/kg/day in 15% of patients with a fatal outcome in 2-3% of affected patients. If hepato-toxicity develops pyrazinamide should be discontinued.[7]

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Material and Methods

The study was conducted at the Medicine Unit, Ayub Teaching Hospital, Abbottabad, and 500 diagnosed cases of tuberculosis were included who were treated with first-line standard anti-tuberculous drugs. Most of the cases included were treated with Isoniazid (INH), Rifampicin, Pyrazinamide (PZA) and Ethambutol. Therapy was initiated with 4 drug regimen, as susceptibility of the clinical isolates could not be determined in our setting, and resistance to INH is not rare.[4]

Informed consent was taken from every patient or his or her caregiver. A comprehensive history of every patient was taken to exclude any hepato-toxicity predisposing factors. The patients were carefully examined for signs of any liver disease, acute or chronic at the outset. Liver function tests (LFT's) including Serum Bilirubin (S. Bil.), Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP) levels of these patients were done before initiation of ATT.[8,9]

The patient and caregivers were educated about the side effects of ATT and told to come at once in case of any untoward effects or evidence of hepatitis. Follow-up clinical examination and Liver Function Tests repeated at 4 and 8 weeks of ATT.

Patients' data was collected and results obtained by analysing the data. The objective of this study was to determine the frequency of ATT-induced hepato-toxicity. This can be a cause of patient morbidity and mortality and lead to non-compliance.

In patients developing hepato-toxicity INH was stopped and patients were restarted on split ATT in which Streptomycin or Ethambutol was used as the fourth drug.[1,2]

Results

Total 500 patients were included in this study. Out of these 277 (55.4%) were males and 223 (44.6%) were females. Forty (8%) patients developed hepato-toxicity, including 20 (7.2%) males and 20 (8.96%) females (Table-1).

Raised transaminases were noted in 19 (3.8%) patients, and 21 (4.2%) patients developed overt hepatitis (7 males and 14 females), out of whom one (0.2%) male died of Acute Fulminant Hepatitis, while 20 improved after excluding INH and giving split ATT (Table-2).

Two hundred and three patients were in the age group between 20-35 years; 8 (3.9%) of them developed mild, 11 (5.4%) developed moderate and none developed severe hepatitis. In the age group 36-50 years, there were 135 patients, out of them 2 (1.47%) developed mild, 2 (1.47%) developed moderate and none developed severe hepatitis. In the age group 51-65 years, there were 141 patients, 6 (4.25%) developed mild, 6 (4.25%) moderate and 1 (0.71%) developed severe hepatitis. Twenty patients were in the oldest age group of >65 years, 3 (15%) developed mild, 1 (5%) moderate and none developed severe hepatitis.

Table-1: Frequency of ATT-Induced Hepatitis.

Development of Hepatitis	Number	%
Absent	460	92.0
ATT Induced Hepatitis	40	8.0

Table-2: Outcome of the study n=500.

Outcome	Number	%
Developed Transiently Raised Transaminases	19	3.8
Developed Overt Hepatitis	21	4.2
Improved After Split ATT Regime	20	4
Expired	1	0.2

Table-3: Age-wise distribution of severity of ATT induced hepatitis (n=40).

		Mild		Moderate		Severe	
Age	Total	Cases	%	Case	%	Cases	%
20–35	203	8	3.9	11	5.4	–	–
36–50	136	2	1.47	2	1.47	–	–
51–65	141	6	4.25	6	4.25	1	0.71
>65	20	3	15	1	5	–	–

Prodromal signs and symptoms and deranged Liver Functions were present in most of the patients presenting with ATT-Induced hepato-toxicity.

Discussion

Tuberculosis is a major cause of preventable infectious disease and death in the world. Timely diagnosis and proper chemotherapy are the mainstays of treatment.

The hepatotoxic side effect of ATT has been under extensive discussion and studies to confirm their frequency and outcome in patients, all over the world. However, it is a surprising fact that most of this research work has been done in the west and in the more developed nations of the world, while studies to the effect have practically never, if ever been done in Pakistan; and especially the northern areas where Tuberculosis, remains a rampant killer to date.

All available data is based on studies conducted in regions having better socio-economic conditions, awareness of impact of disease and having better patient education about possible side-effects and follow-up facilities as well as better patient compliance thus resulting in lesser frequency of hepatitis.

In a similar rare study conducted by Haq MU et al10 on One hundred and sixty seven (167) consecutive patients admitted in Institute of Chest Medicine, Mayo Hospital, Lahore during

the months of June, July and August 1998 with diagnosis of pulmonary and/or extra pulmonary Tuberculosis. Liver function tests including serum bilirubin, S. alkaline Phosphatase, SGOT and SGPT were done at the start of treatment. They were all prescribed Rifampicin, Isoniazid Ethambutol and Pyrazinamide. Incidence of hepato-toxicity was studied in the subjects of this study in relation with the age, sex, extent of disease, duration of ATT. It was found that incidence of hepato-toxicity is higher in those older than 35 years and females are more commonly affected. 11 patients had hepato-toxicity. Out of 11 patients, three died during treatment, jaundice cleared in remaining 8 patients in 7-15 days. In our study frequency of ATT-Induced hepato-toxicity was more in ages more than 35 years and of increasing severity. There was greater female preponderance. This can however also be explained on the basis of a larger number of patients in this group.

In a study by Shakya et al8 to determine the incidence of antitubercular drug-induced hepatotoxicity in a Nepalese urban population. Fifty patients diagnosed with active tuberculosis infection with normal pre-treatment liver function were monitored clinically as well as bio-chemically in a prospective cohort analysis. ATT was found to be associated with derangement of hepatic function, resulting in elevation of liver enzymes to a variable extent. Thirty eight percent of patients had 2 times and 30% had more than 3 times elevation of ALT. Four patients (8%) developed drug-induced hepato-toxicity. The time interval for onset of hepatotoxicity after initiation of therapy was 12-60 days. ATT-induced hepato-toxicity was found more often in younger patients. Female gender was also a higher risk. A finding of an 8% incidence of hepato-toxicity is considerably high. Risk factors of hepato-toxicity included female gender, disease extent, and poor nutritional status. Timely detection and temporary withdrawal of the offending agent can completely cure ATT-induced hepato-toxicity.

In a study done by Jagdeep Singh et al11 on seventy-two consecutive patients with clinical evidence of ATT-induced hepato-toxicity, jaundice was the presenting symptom in 44 (61%) patients; prodromal symptoms were present in 28 (39%), serious complications developed in 12 (16.6%) patients (fulminant hepatic failure in seven, subacute hepatic failure in four, hepatic encephalopathy in one), 9 patients (3 males, 6 females) died from these complications. In their study, the mean duration of treatment before the onset of hepatitis was significantly longer in the group that died than in the rest of the patients; after resolution of ATT-induced hepatitis, reintroduction of isoniazid and rifampicin was possible in 41 of 44 patients; thus, their results showed that ATTinduced hepato-toxicity carried significant morbidity and mortality. They reintroduced ATT safely after recovery from hepatitis. In our study 21 patients presented with jaundice, nausea and vomiting and one patient died of FHF. Treatment with ATT excluding INH was done in 24 patients with success in our study group.

Conclusion

ATT can be a cause of hepato-toxicity in up to 5 percent of patients. It causes fatal liver damage in up to 0.2 percent of patients. If patients are not properly monitored, as is often the case, in our setting, fatal results can occur. Moreover the patients may stop taking drugs and resultant latent TB or MDR can occur.

All patients put on ATT must be followed up for at least the initial 3 weeks, and the patient and caregivers should be told how to recognize signs of ATT-induced hepato-toxicity. The patients and the doctors have to be well-educated about the adverse effects of the ATT, its early recognition and management.

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