ORIGINAL ARTICLE

Determine the Hepatotoxicity with Anti-Tuberculosis Drugs and its Severity and Frequency

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ABSTRACT

Aim: To measure the frequency and severity of hepatotoxicity caused by various anti-tuberculosis (ATT) drugs and assess whether concurrence of risk factors impact the hepatotoxicity induced by anti-tuberculosis drug.
Study Design: Prospective cohort study.
Place and duration of study: Department of Medicine, Lady Reading Hospital, Peshawar from 1st March 2018 to 28th February 2019.
Method: A total of 350 patients were observed who were identified with active tuberculosis infection with clinical and biochemical normal liver function. The data was collected and the patients were treated with Isoniazid, rifampicin and pyrazinamide. The time later to imbalance in function, if any, happened and time required for regularization was calculated. If necessary, the treatment was changed, except for the harmful drug.
Results: Seventy one (20.3%) patients have ATT-induced hepatotoxicity. Women were more affected than men (27% vs. 20%). BMI (kg/m2) of 92% in the patient group, was less than 18.3 ($p < 0.01$), many of them had anemia and suggested low albumin mass. In patients with positive AFB smear; there was more severe hepatotoxicity noted. Simultaneous use of low serum cholesterol, paracetamol and alcohol has been shown to be predisposing factors. The main culprit was isoniazid 40(56.3%) patients, $p < 0.01$] charted by pyrazinamide 10(14.08%) and rifampicin 25(35.21%) patients. Many of the subjects included (61%) experienced mild to moderate hepatotoxicity with ALT and AST within 2 weeks of initial to treatment of tuberculosis.
Conclusion: Anti-tuberculosis treatment persuaded hepatitis is very common and have much serious effects in cases with risk factors for hepatotoxicity.
Keywords: Anti-tuberculosis drugs, Hepatotoxicity, Risk factors, Tuberculosis

INTRODUCTION

Tuberculosis has proved to be a common infectious disease that threatens the human population, especially developing countries[1]. World Health Organization has announced that tuberculosis is a universal threat. Operative control has been attained due to the extensivespread of anti-tuberculosis treatment. Though, in spite of its effectiveness, it is necessary to overcome the problems associated with the long course of treatment, the appearance of MDR strains and the appearance of some negative effects attributed to these drugs[2-3]. Amongst these negative effects, a well-known complication of anti-tuberculosis therapy (ATT) is hepatotoxicity. The severity varies from variation in liver enzymes, picture of acute hepatitis, chronic active hepatitis and infrequently problematic by acute liver failure causing very high death ratiolest transplanted. It is communal for isoniazid, specifically when taken in amalgamation with pyrazinamide and rifampicin. Serum alanine and aspartate transaminase levels may increase in 15-25% who were taking isoniazid as only TB agent, but only 1 percent may have severe hepatic necrosis. The drug-induced hepatotoxicity histopathological, biochemical and clinical features are not differentiable from hepatitis related to virus. In Pakistan; tuberculosis is a communal problem. We don't have accurate data on drug-induced hepatitis in Pakistan[4-5].

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In patients at high risk of hepatotoxicity due to tuberculosis and thus reducing morbidity and mortality, the treatment regimen should be established and changed early[6].

It is assumed that the hepatotoxicity caused by ATT is not really unique. On the contrary, it has been discovered that some genetic and environmental factors overlap to produce enough noxious metabolites that source various changes in liver function. In the liver; ATT inducible cytochrome P-450 2E1 (cyp2E1) is expressed constitutively[7-8]. Current analysis display that the N-acetyl transferase 2 (NAT2) polymorphism and glutathione s transferase genes are 2 important possibility factors for hepatotoxicity induced by ATT. The hepatotoxicity risk factors are: advanced age, poor nutrition, female sex, existing liver disease, high alcohol consumption, hypoalbuminaemia, hepatitis B in developing countries and drug abuse and advanced tuberculosis[9].

We conducted this study in several variety of TB patients who received ATT to determine the frequency and severity of hepatotoxicity and the association between sex, age, alcoholism, nutritional status, cholesterol levels and hepatitis induced with drugs.

MATERIALS AND METHODS

This prospective cohort study was held in the Medicine department of Lady Reading Hospital, Peshawar for one year duration from 1st March 2018 to 28th February 2019 and 350 patients were selected according to inclusion and

exclusion criteria. Amongst extra pulmonary envelopment cases were differentiated such as that of bones/ spine, abdomen, lymph nodes, meninges, skin, genital, pericardium, joints or miliary dissemination. Only tuberculosis patients were considered eligible for recruitment who received rifampicin, isoniazid, pyrazinamide and ethambutol by body weight as part of the treatment regimen. Patients treated with anti-tuberculosis therapy were not selected for the study if they had one of the subsequent symptoms: patient'swho had previously had acute or chronic liver disease, baseline transaminase, treated with rifampin and isoniazid and fatty liver.

The liver function status, BMI and body weight, concurrent pharmacological treatment or alcoholism history and laboratory investigations, specially serum albumin, hemoglobin, LFT, serum cholesterol and abdominal ultrasound were done all patients. Malnutrition was definite as less than 18.5 BMI (kg/m2). To eliminate viral hepatitis patients; Viral markers were done. The ultrasound was done to exclude fatty liver. During the 1st month; LFT was done twice in a week, then two times in a month and then monthly until the end of anti-tuberculosis therapy. A nine-month general treatment period followed by a two-month intensive phase and a seven-month control phase. The Intensive phase consists of daily rifampicin (R), isoniazid (INH), ethambutol (E) and pyrazinamide (Z). Streptomycin (S) was started as the first treatment régime, and ethambutol changed as needed. The continual phase includes daily isoniazid and rifampicin. Doses of the drug: rifampicin 10 mg/kg/day, INH 5 mg/kg/day (maximum 300 mg / day), ehambutol 15 mg / kg / day, pyrazinamide 20-25 mg / kg / day and 15 mg / kg / day; streptomycin was given. Hepatotoxicity is definite as the regularization of liver function after discontinuation of all ATT drugs and the occurrence of minimum one of the subsequent criteria: (1) jaundice (2) increased serum AST and / or ALT five times more than its limit (50 IU/l); (3) increase in total serum bilirubin> 1.5 mg/dl9. SPSS version 19.0 was applied for statistical analysis.

RESULTS

There were 180(51.4%) male patients and 170(48.5%) were females. Patient ages ranged from 13 to 75 years old with 37 years average age. The patient's body weight exhibited a widespreaddisparity with 20kg and 86kg at the two extremes and 30kg was the mean body weight. Preliminary biochemical estimation showed hemoglobin from 6.10 to 11.5 gm, SGPT from 23 to 57 IU and serum cholesterol from 100 to 250 mg. The alcoholic dependent patients were eight and nearly all subjects used paracetamol for numerous purposes (Table I).

Patients with extrapulmonary and pulmonary tuberculosis were included in the study. While lung involvement was noted in about 51.4% (180 patients), the remaining 17% abdomen (60 patients), 8.9% meninges (31 patients), lymph node involvement in 7.2% (25) patients were the main varieties (Table II).

Throughout the study time, 71(20.3%) of 350 people taking anti-tuberculosis drugs developed hepatotoxicity, which was determined based on clinical studies and established by LFTS. All these patients differed in SGOT and SGPT, but the mainstream of 40 patients (11.4%) experienced a slight change 3 to 5 times than usual. 16 patients had severe disorders in SGOT and SGPT, and 18 patients had moderate disorders. In 34 patients; Bilirubin levels were raised, and 21had slightly increased to 3 g in most patients and above 3g noted in 13 patients (Table 3).

Table 1: Demographic information of the patients

Variable	Range	Average
Gender	M=180, F=170	
Age (years)	13-75	37
HB (gm%)	6.10- 11.5 gm	8.4
Body weight (kg)	20-86	30
LFTs (SGPT) (I.U)	23- 57	
H/o alcoholism	8 patients	
Serum cholesterol	100-50(mg%)	137
Concomitant paracetamol intake	All patients	

Table 2: Different varieties of TB and associated hepatotoxicity

Type	No.	%	Hepatotoxicity	%
Abdominal	60	17.0	28	47.0
Pulmonary	180	51.4	24	13.3
TBM	31	8.9	6	19.3
Spine/Bone	20	5.8	4	20
Lymph node	25	7.2	3	12.0
Miliary	11	3.1	3	27.0
Genital	5	1.4	1	20.0
Joints/Arthritis	7	2.0	1	14.3
Skin	5	1.4	-	-
Pericardial effusion	6	1.7	1	16.7

Table 3: ATT Induced Alterations in LFTs (hepatotoxicity occurred in 71 out of 350 patients: 20.3%)

Variable	Patients	No. (%)
SGPT (n=71)	Mild 3 to 5 times of normal (15-40)	40(11.4%)
	Moderate 5 to 10 times of normal (201-400)	18 (5.14%)
	Severe >10 times of normal >400	16 (4.6%)
SGPT (n=71)	2 to 5 times of normal	40(11.4)
	5 to 10 times of normal	18(5.14)
	>10times of normal	16(4.6)
Bilirubin (n=34)	2 to 3 mg%	21(6)
	> 3 mg%	13(3.7)

Female sex was 24% (40 out of 170) more than men (43 out of 180) compared with 23.8%. Due to hepatotoxicity caused by ATT, older patients were comparatively more affected than the young age group. The time from the start of treatment to the start of hepatotoxicity was documented. The maximum patient's number (43 out of 71) established hepatotoxicity at the beginning of 14 days of treatment. 21 patients had hepatic impairment within 2-4 weeks, while the remaining patients had abnormalities after one month of treatment. Liver function tests were normalized in approximately four-fifths of patients over two weeks.The main culprit was isoniazid 40(56.3%), p <0.01] charted by pyrazinamide 10(14.08%) and rifampicin 25(35.21%) patients.

DISCUSSION

In the world; tuberculosis dissemination is an economic and social burden, particularly for under developed countries, and the usage of anti-tuberculosis drugs is an enthusiastic method to resolve this issue. However, some warnings

regarding its use should be adequately assessed, in particular liver damage due to ATT and factors susceptible to this hepatotoxicity[10-11].

This analysis was held to evaluate the effects of risk factor such as age, gender, disease severity, nutritional status, alcoholism, paracetamol use and anti-tuberculosis drugs encouraged hepatotoxicity. 21 % of patients established anti-tuberculosis drugs- persuaded hepatotoxicity in this study, which is virtually the same as in Japan[12]. The multi-drug therapy combination for tuberculosis is related with an increased hepatotoxicity risk paralleled to INH monotherapy for the prevention of tuberculosis. Although the incidence of ATT-induced hepatotoxicity is not fully understood, it varies in many countries, but the risk factors and characteristics of the study population may differ from the altered diagnostic standards used to describe hepatotoxicity, geographical tests and monitoring type[13].

In our analysis, hepatotoxicity induced by ATT in 40 patients and isoniazid was the main culprit, although it was the backbone of tuberculosis treatment. Isoniazid may cause a small asymptomatic change in the liver enzyme that does not necessitate termination of the medicines in the first days of treatment. INH causes hepatotoxicity as a result of idiosyncratic reactions[14]. The isoniazid, pyrazinamide and rifampicin given in combination rises the anti-tuberculosis persuaded hepatotoxicity risk. Rifampicin is a comparatively acquitted drug compared to isoniazid, but there were 25 patients (36%) suffering anti-tuberculosis treatment induced hepatotoxicity. Isoniazid is a strong enzyme inducer that can increase hepatotoxicity[15]. Pyrazinamide also encompass seven patients (10.5%) and represents the majority of hepatotoxic anti-tuberculosis drugs such as isoniazid. It is believed that the mechanism of hepatotoxicity is the dose associated, but one case reported difficulties after the first reaction to the given in combination, leading to the rise in serum transaminase levels up to 80 times the normal upper limits. This is normal for eosinophils associated with a hypersensitivity reaction.

CONCLUSION

Hepatotoxicity caused by ATT can cause permanent injury and death. In the event of an immediate withdrawal of an aggressive agent, early diagnosis is necessary to stop its progress and permit the liver to reconcile. Therefore, the precise relationship of influencing factors that may increase liver damage in the ATT-treated populace may indicate that patients sensitive to their development should be closely monitored for hepatotoxicity and develop a new treatment regimen as soon as possible and reduce the burden of morbidity and mortality caused by commonly used anti-tuberculosis drugs.

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