TO OBSERVE THE HEPATOTOXICITY WITH ANTI-TUBERCULOSIS DRUGS AND ITS FREQUENCY AND SEVERITY.

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ABSTRACT

OBJECTIVE: To measure the frequency and severity of hepatotoxicity caused by various antituberculosis drugs (ATTs). Study design: prospective cohort study. **PLACE AND DURATION:** In the Medicine ward of Bilawal Medical College Hospital Kotri one-year duration from April 2019 to April 2020. **METHOD:** A total of 450 patients with active tuberculosis infection with normal clinical and biochemical liver function were observed. Data were collected and patients were treated with isoniazid, rifampin, Ethambutol and pyrazinamide. The time after the imbalance, if any, in the function was calculated and the time required for regulation was calculated. Treatment was changed if necessary, except for harmful drugs. **RESULTS:** There were 230 (51.11%) male and 220 (48.88%) female patients. The ages of the patients ranged from 14 to 76, with an average age of 38. The preliminary biochemical estimate showed 6.15 to 12.6 g of hemoglobin, 25 to 59 IU of SGPT, and 100 to 250 mg of serum cholesterol. There were nine patients with alcohol dependence, and almost all subjects used paracetamol for various purposes. During the study period, 86 (19.11%) of 450 people using anti-tuberculosis drugs developed hepatotoxicity determined by clinical studies and by LFTS. All of these patients differed in SGOT and SGPT. The patients had severe impairments in SGOT and SGPT. Women were 22.72% (50 out of 220) more than men (44 out of 230) 19.19%. Due to the hepatotoxicity caused by ATT, elderly patients are relatively more affected than the younger age group. The time elapsed from the start of treatment to the onset of hepatotoxicity has been documented. The maximum number of patients caused hepatotoxicity at the start of treatment 14 days. While 29 patients developed liver failure within 2-4 weeks, the remaining patients developed abnormalities after one month of treatment. Liver function tests normalized in approximately four-fifths of the patients over two weeks. The main culprit was isoniazid 60 (69.76%) followed by pyrazinamide, p <0.01]. **CONCLUSION:** Antituberculus therapy induced hepatitis is very common and has serious effects of hepatotoxicity in patients.

KEYWORDS: Antituberculosis Drugs, Hepatotoxicity, Risk Factors, Tuberculosis

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INTRODUCTION

Tuberculosis has proved to be a common infectious disease threatening the human population, particularly in developing countries[1]. The World Health Organization announced that tuberculosis is a universal threat. Medical control has been achieved thanks to the wide spread of anti-tuberculosis therapy. Despite its effectiveness, long-term treatment is necessary to overcome the problems associated with the emergence of MDR strains and the emergence of some of the adverse effects attributed to these drugs[2-3]. Among these adverse effects, a well-known complication of tuberculosis therapy (CAM) is hepatotoxicity. It differs in severity from variation in liver enzymes, acute hepatitis, chronic active hepatitis and, rarely, problems related to acute liver failure, which causes a very high mortality rate for non-transplantation. It is common for isoniazid, especially when taken in amalgam with pyrazinamide and rifampin. Serum alanine and aspartate transaminase levels may increase in 15-25% of those taking isoniazid as the sole antituberculous agent, but only 1% may have severe liver necrosis. The histopathological, biochemical and clinical features of drug-induced hepatotoxicity cannot be distinguished from virus-associated hepatitis. In Pakistan; tuberculosis is a social problem. We do not have accurate data on drug-related hepatitis in Pakistan[4-5].In patients with a high risk of hepatotoxicity due to tuberculosis and therefore 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 truly unique. On the contrary, it has been found that certain genetic and environmental factors overlap to produce metabolites harmful enough to cause various changes in liver function. In the liver; ATT-inducible cytochrome P-450 2E1 (cyp2E1) is

constitutively expressed[7-8]. Current analysis shows that the N-acetyl transferase 2 (NAT2) polymorphism and glutathione transferase genes are two important probability factors for ATT-induced hepatotoxicity. Risk factors for hepatotoxicity are: advanced age, malnutrition, female gender, current liver disease, high alcohol consumption, hypoalbuminemia, hepatitis B, C and drug use in developing countries, and advanced tuberculosis[9-12].

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

MATERIALS AND METHODS

This prospective cohort study was conducted for one year from April 2019 to April 2020 at Medical ward of Bilawal Medical College Hospital Kotri and 450 patients were selected based on inclusion and exclusion criteria. Bone / spine, abdomen, lymph nodes, meninges, skin, genitals, pericardium, joints, or miliary dissemination among cases of extrapulmonary envelopment were included. Only tuberculosis patients who received rifampicin, isoniazid, pyrazinamide, and ethambutol by body weight as part of the treatment regimen were eligible for enrollment. Patients treated with antituberculosis therapy were not selected for the study if they presented one of the following symptoms: patients with previous acute or chronic liver disease, patients treated with rifampin and isoniazid, and fatty liver.Laboratory examinations such as liver function status, BMI and body weight, concomitant drug therapy or history of alcoholism and especially serum albumin, hemoglobin, LFT, serum cholesterol and abdominal ultrasound were performed in all patients. Malnutrition was defined as below 18.5 BMI (kg / m2). Eliminate patients with viral hepatitis; Viral markers were made. Ultrasound was done to exclude fatty liver. During the first month; LFT was performed twice a week, then twice a month, and then once a month until the end of antituberculosis therapy. A nine-month general treatment period, by a two-month intensive phase and a seven-month continuous phase. The dense phase consists of rifampicin (R), isoniazid (INH), ethambutol (E) and pyrazinamide (Z) daily. Streptomycin(S) was initiated as the initial treatment regimen and ethambutol was modified as needed. Continuous phase includes daily isoniazid and rifampicin. Drug dosage: rifampicin 10 mg / kg / day, INH 5 mg / kg / day (maximum 300 mg / day), ethambutol 15 mg / kg / day, pyrazinamide 20-25 mg / kg / day and 15 mg / kg / day streptomycin was applied. Hepatotoxicity is defined as regulation of liver function after discontinuation of all ATT drugs and the occurrence of at least one of the following criteria: (1) jaundice (2) from the five-fold limit of increase in serum AST and / or ALT (50 IU / l); (3) increase in total serum bilirubin> 1.5 mg / dl9. SPSS version 23.0 was applied for statistical analysis.

RESULTS

There were 230 (51.11%) male and 220 (48.88%) female patients. The ages of the patients ranged from 14 to 76, with an average age of 38. The patient's body weight showed wide disparity with 22 kg and 96 kg at both ends, and the average body weight was 33 kg. The preliminary biochemical estimate showed 6.15 to 12.6 g of hemoglobin, 25 to 59 IU of SGPT, and 100 to 250 mg of serum cholesterol. There were nine patients with alcohol dependence, and almost all subjects used paracetamol for various purposes (Table I).

Patients with extrapulmonary and pulmonary tuberculosis were included in the study. Approximately 42.2% (190 patients) had lung involvement, 15.6% (70 patients) abdominal,tuberculous meningitis 9.1% (40 patients),7.8% (35 patients)had lymph node involvement, while the miliary involvement were 4.7% (21) patients (Table II).During the study period, 86 (19.11%) of 450 people using anti-tuberculosis drugs developed hepatotoxicity determined by clinical studies and caused by LFTS. All of these patients differed in SGOT and SGPT. The patients had severe impairments in SGOT and SGPT are given in Table 3.Women were 22.72% (50 out of 220) more than men (44 out of 230) 19.19%. Due to the hepatotoxicity caused by ATT, elderly patients are relatively more affected than the younger age group. The time elapsed from the start of treatment to the onset of hepatotoxicity has been documented. The maximum number of patients caused hepatotoxicity at the start of treatment 14 days. While 29 patients developed liver failure within 2-4 weeks, the remaining patients developed abnormalities after one month of treatment. Liver function tests normalized in approximately four-fifths of the patients over two weeks. The main culprit was isoniazid 60 (69.76%) followed by pyrazinamide, p <0.01].

Table 1: Demographic information of the patients

Variable	Range	Average
Gender	M=230, F=220	
Age (years)	14-76	39
Hb (gm%)	6.15- 12.6 gm	8.6
Body weight (kg)	22-93	33
LFTs (SGPT) (I.U)	25- 59	
H/o alcoholism	9 patients	
Serum cholesterol	100-150(mg%)	148
Concomitant paracetamol intake	All patients	

Table 2: Different varieties of TB and associated hepatotoxicity

Type	No.	%	Hepatotoxicity	%
Abdominal	70	15.6%	31	44.3%
Pulmonary	190	42.2%	26	13.7%
TBM	41	9.1%	7	17.1%
Spine/Bone	30	6.7%	6	20.0%
Lymph node	35	7.8%	5	14.3%
Miliary	21	4.7%	5	23.8%
Genital	15	3.3%	2	13.3%
Joints/Arthritis	17	3.8%	2	11.8%
Skin	15	3.3%	-	0.0%
Pericardial effusion	16	3.6%	2	12.5%

Table 3: ATT Induced Alterations in LFTs (hepatotoxicity occurred in 86 out of 450 patients: 20.3%)

Variable	Patients	No. (%)
SGOT (n=71)	Mild 3 to 5 times of normal (15-40)	50 (11.11)
	Moderate 5 to 10 times of normal (201-400)	28 (6.22%)
	Severe >10 times of normal >400	6 (5.78%)
SGPT (n=71)	2 to 5 times of normal	50 (11.11)
	5 to 10 times of normal	28 (6.22)
	>10times of normal	26 (5.78)
Bilirubin (n=34)	2 to 3 mg%	31 (6.89)
	> 3 mg%	23 (5.11)

DISCUSSION

In the world; spread of tuberculosis is an economic and social burden, especially for underdeveloped countries, and the use of anti-tuberculosis drugs is an enthusiastic method to solve this problem. However, some warnings regarding its use, especially liver damage caused by them and factors sensitive to this hepatotoxicity should be appropriately evaluated[12-13].This analysis was conducted to evaluate the hepatotoxicity inducing effects of risk factors such as age, gender, disease severity, nutritional status, alcoholism, paracetamol use and antituberculous drugs. In this study, which is practically the same as in Japan, 21% of patients convinced hepatotoxicity due to antituberculous drugs. The combination of multiple drug therapy for tuberculosis is associated with an increased risk of hepatotoxicity in parallel with INH monotherapy for tuberculosis prevention[14-15]. Although the incidence of hepatotoxicity caused by ATT is not fully understood, it varies in many countries, but the risk factors and characteristics of the study population differ from the modified diagnostic standards used to describe hepatotoxicity and geographic testing[16-17].In our analysis, although it is the backbone of tuberculosis treatment, ATT-induced hepatotoxicity and isoniazid were the main culprits in most patients. Isoniazid may cause a small asymptomatic change in the liver enzyme that does not require discontinuation of the drugs during the first few days of treatment. INH causes hepatotoxicity as a result of specific reactions[18]. Concomitant isoniazid, pyrazinamide and rifampicin increase the risk of hepatotoxicity against tuberculosis. Rifampicin is a comparatively cleared drug compared to isoniazid, but there were 25 patients (36%) suffering from hepatotoxicity due to antituberculous therapy. Isoniazid is a potent enzyme inducer that can increase hepatotoxicity[19-20]. Pyrazinamide also represents the majority of hepatotoxic antituberculous drugs such as isoniazid. The mechanism of hepatotoxicity is believed to be the dose associated but one case reported difficulties after the initial reaction to the administered combination, leading to an increase in serum transaminase levels to 8 times the upper normal limits[21-22]. This is normal for eosinophils associated hypersensitivity reaction.

CONCLUSION

Hepatotoxicity caused by ATT can cause permanent injury and death. In case of immediate suspension of an aggressive agent, early diagnosis is required to halt its progression and allow the liver to reconcile itself. Therefore, the precise relationship of factors that can increase liver damage in the ATT-treated population may indicate that patients susceptible to its 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.

ETHICS APPROVAL: The ERC gave ethical review approval **CONSENT TO PARTICIPATE:** written and verbal consent was taken from subjects and next of kin**FUNDING:** The work was not financially supported by any organization. The entire expense was taken by the authors**ACKNOWLEDGEMENTS:** We would like to thank the all contributors and staff and other persons for providing useful information.**AUTHORS' CONTRIBUTIONS:** All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.**CONFLICT OF INTEREST:** No competing interest declared.

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