Original Article

# Standard Antituberculosis Drug Induced Hepatotoxicity: Do the Risk Factors Matter?

Haji Khan Khoharo, Shuaib Ansari, Ali Akber Siddiqui, Fatima Qureshi

## ABSTRACT

**OBJECTIVE: To determine the frequency of hepatotoxicity with standard antituberculosis drug therapy and its risk factors.**

**METHOD: This prospective cohort study was conducted at Muhammad Medical College Hospital, Mirpurkhas and Liaquat University Hospital Jamshoro, from July 2007 to August 2008. A total of 350 cases of active pulmonary tuberculosis with normal pretreatment liver function test (LFT) were selected through probability sampling. Patients were started first line antituberculosis drug therapy (ATT). The liver function derangement was monitored. If any hepatotoxicity noticed, the time duration for toxicity occurrence and time taken for normalization of LFT were recorded. ATT was altered as needed, with exclusion of toxic drug. Data were collected on proforma and analyzed by using SPSS version 10.0.**

**RESULTS: ATT induced hepatotoxicity developed in 91 (26%) patients with minor, moderate and severe alanine transaminase (ALT) rise noted in 48 (52.75%), 40 (43.95%) and 3 (3.3%) cases respectively. Hepatotoxicity for individual drugs were noted as; Isoniazid (INH) 53 (58.24%), rifampicin 32 (35.16%) and pyrazinamide (PZA) 6 (6.59%) (p=0.01). Malnutrition, low albumin, acetaminophen, female sex, older age and low serum cholesterol were noted as the risk factors (p=0.05)**

**CONCLUSION: Hepatotoxicity occurs significantly with anti-TB drugs, usually reversible and rarely fulminant. It is more frequent in patients with malnutrition, low albumin, acetaminophen, female sex, older age and low serum cholesterol**

**KEY WORDS: Pulmonary tuberculosis, Anti-TB drugs, Hepatotoxicity, Risk factors.**

## INTRODUCTION

Tuberculosis (TB) is a major cause of illness and death worldwide, especially in Asia and Africa. Globally 9.2 million new cases (139 per million population), including 4.1 million new smear-positive cases (44% of the total) and 1.7 million deaths from TB occurred in 2006, of which 0.7 million cases and 0.2 million deaths were in HIV-positive people[1]. This is an increase from 9.1 million cases in 2005, due to population growth. In Pakistan, the prevalence of tuberculosis reported in 2006 was 263 cases per million population and the incidence of 181 per million population per year[1]. An effective control has been achieved by the widespread use of ATT. Among the adverse effects, hepatotoxicity is a well known complication of ATT [2-3]. The severity ranges from alteration in liver enzymes, chronic active hepatitis and acute hepatitis, occasionally complicated by acute liver failure carrying very high mortality unless transplanted. It is common with INH especially when given in combination with rifampicin and PZA. Fifteen to 20 percent of patients receiving INH as a single agent for prophylaxis against tuberculosis may have increased serum alanine (ALT) and aspartate aminotransferase (AST) levels, but only 1 percent have hepatic necrosis severe enough to require the withdrawal of the drug[4]. It has been postulated that hepatotoxicity induced by ATT is not truly idiosyncratic in essence; rather certain genetic and environmental factors are attributed to coincide to produce sufficient quantity of toxic metabolites that then cause varied alterations in liver functions. ATT inducible cytochrome P-450 2E1 (cyp2E1) is constitutively expressed in the liver.[5] Recent studies show that polymorphism of the N-acetyltransferase-2 (NAT-2) genes and glutathione-s transferases (GST) are the two major susceptibility risk factors for ATT induced hepatotoxicity[6]. The underlying mechanisms of ATT induced hepatotoxicity and the factors predisposing to its development are not clearly understood. The age, sex, poor nutritional status, chronic alcoholism, pre-existing liver disease, hypoalbuminaemia, advanced tuberculosis, acetaminophen, inappropriate use of drugs and acetylator status have all been incriminated as possible predisposing factors in earlier studies[7]. Acetaminophen is metabolized mainly by glucuronidation and sulfation, with a small fractin metabolized via the CYP2E1 to a highly recative toxic metabolite that is nomally detoxified by the cellular glutathione. Patients with enhanced CYP2E1 such as chronic alcoholics and patients taking INH are at increased risk of developing

hepatotoxicity[8]. Rifampicin induces the CYP2E1 activity thereby increases the INH related hepatotoxicity[9]. As the tuberculosis is very common in Sindh, we planned to conduct a prospective study at tertiary care level to know the frequency of ATT induced hepatotoxicity and its risk factors.

## PATIENTS AND METHODS

This prospective cohort study was conducted at Muhammad Medical College Hospital Mirpurkhas and Liaquat University Hospital Jamshoro covered period from July 2007 to August 2008. A total of 350 diagnosed cases of active pulmonary tuberculosis, both male and female, were selected through probability sampling, and prescribed first line ATT. Following patients were excluded form the study: ATT drug defaulters/chronic cases, preexisting acute or chronic liver disease, pretreatment transaminases more than two times normal, extrapulmonary tuberculosis, positive viral markers for HBV and HCV, and fatty liver. All patients were evaluated for hemoglobin levels, viral markers, serum albumin, serum cholesterol, LFTs and ultrasound abdomen. Malnutrition was defined as BMI <18.5 (kg/m2). LFTs were repeated weekly for the first month then twice in next month and thereafter monthly till the completion of ATT. ATT induced hepatotoxicity was defined as normalization of liver function after withdrawal of all anti-tuberculosis drugs, and the presence of at least one of the following criteria: (1) appearance of jaundice (2) a rise of five times the upper limit of normal levels (50 IU/L) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT); (3) a rise in the level of serum total bilirubin >1.5mg/dl[10]. In patients having minor distarbance in liver enzymes upto 3-5 times of normal, ATT was continued but with moderate distarbance i.e. 5-10 times of normal, were closely observed for signs of acute/ fulminant hepatitis or further rise in enzymes or appearance of jaundice. In such patients ATT was withheld and patients were followed with repeated LFTs till normalization, after which ATT was reintroduced with PZA followed by rifampicin and then INH. In case patient again developed symptoms or signs of hepatotoxicity, the causative drug was then permanently excluded from the treatment. Total treatment period of seven months comprising intensive phase of two months of daily INH, rifampicin (R), PZA (Z) and ethambutol (E), and continuation phase of five months of daily INH and rifampicin. Streptomycin (S) was added to the initial treatment regimen replacing ethambutol whenever necessary. The dosages of drugs were: INH 5mg/kg/day (maximum 300-mg/day), rifampicin 10-mg/kg/day, pyrazinamide 20-25-mg/kg/ day, ethambutol 15-mg/kg/day and streptomycin 15mg/kg/day. A predesigned proforma was used to record the data regarding socio-demomographical characteristics, baseline investigations, LFT, ALT, serum cholesterol, drug intake. Change in ALT level after iniatiating treatment and occurance of hepatotoxicity were also noted. Descriptive statistical analysis was performed by using SPSS V.11. Chi-square test was applied and P-value up to 0.05 was considered significant.

## RESULTS

Total 350 patients were included in this study. Males were 195 (55.72%) and female were 155 (44.28%) with overall mean age of 34.62±8.3 years. **Table I** details the baseline characteristics and biochemical evaluation of 350 subjects. During the course of the study hepatotoxicity was developed in 91 (26%) cases. **Table II** Shows ALT changes and toxicity of different drugs. The hepatotoxicity was recorded in 49 (53.85%) patients within 2 weeks, in 23 (25.27%) patients within 2-4 weeks and in 19 (20.88%) patients after 4 weeks. Bilirubin levels increased in 53 (58.24%) patients with majority, i.e. 49 (53.85%) showing mild increases of up to 3-g%. Liver function was normalized in 86 (94.5%) patients within 2 weeks. Albumin level >3.5-g/dl were seen in 75%, suggestive of lean body mass that predisposes for hepatotoxicity. Acute fulminant hepatitis was not seen in our study. Hypocholesterolemia was noted in 26 (7.43%), out of which 16 patients (61.54%) developed hepatotoxicity, whereas 75 (23.15%) patients of normal cholesterol level also developed hepatotoxicity (p=0.05). Female sex was more affected as compared to males; 51 (32.9%) out of 155 vs. 40 (20.51%) out of 195 (p=0.05). Patients of old age were relatively more affected than the younger age group (p<0.05). Acetaminophen intake of 2-g daily caused hepatotoxicity in 37% of patients. In our study hepatotoxicity was not observed in any of the three alcoholic patients.

**TABLE I: DEMOGRAPHIC DATA & BASELINE LAB. VALUES OF STUDY GROUP (n=350)**

| | |
|---|---|
| Age | 34.62±8.30 (range 20-44 years) |
| Sex | M 195 (55.71%) F 155 (44.28%) |
| Body weight | 42±5.5kg (range 35-63 kg) |
| BMI | <18.5 (kg/m2) in 70% |
| Hemoglobin | 10.5±2.78 g% |
| Alanine transaminase (ALT) | 37±10 I.U |
| Albumin | 3±1.58g% |
| Bilirubin | 1± 0.7 mg% |
| Serum Cholesterol | 125±75 mg% |
| Acetaminophen intake | 350 (100%) |

**TABLE II: ALANINE TRANSAMINASE (ALT) CHANGES & DRUG TOXICITY (n=91)**

| | |
|---|---|
| Minor ALT change (3-5 times) | 48 (52.74%) |
| Moderate ALT change ( 5-10 times) | 40 (34.95%) |
| Severe ALT change (>10 times) | 3 (3.29%) |
| Isoniazid | 53 (58.24%) |
| Rifampicin | 32 (35.16%) |
| Pyrazinamide | 6 (6.59%) |

## DISCUSSION

This study was conducted to determine the frequency and role of age, sex, nutritional status, alcoholism, use of acetaminophen, serum albumin and cholesterol level as a risk factor for ATT induced hepatotoxicity. The frequency of ATT induced hepatotoxicity found in this study was 26% comparable to those reported in the Asian countries, ranging 8-39% compared to developed countries at 3-4% despite similar regimens used [11,12]. Our study has clearly shown the higher incidence of ATT induced hepatotoxicity in females as compared to males (32.9% vs. 20.5%) and these result match with previous studies.[13,14] Vulnerability of females may be due to variations in pharmacokinetics and slow acetylation enzymatic pattern, resulting in hepatotoxicity[15]. Older age group was affected more as compared to younger one strengthening the previous studies[16]. Hemoglobin levels of 76% patients fall in the category of moderate to severe anemia. Nutritional status of our patients was very poor and 70% patients having BMI below 18.5 ($kg/m^2$) and 75% of the patients showed hypoalbuminaemia; this may be one of the risk factors of ATT induced hepatotoxicity[17,18]. The possible explanation of ATT induced hepatotoxicity in malnutrition is depletion of glutathione stores that makes one vulnerable to oxidative injuries. Our study depicts the same result as one from India showing three times higher incidence of ATT induced hepatotoxicity in malnourished patients[19]. Concomitant use of acetaminophen predisposes for the liver injury. Alcoholism was not proved to be the predisposing factor for hepatotoxicity [16,17]. ATT induced hepatotoxicity was seen in 61.53% of the patients with decreased cholesterol level. However further studies are required for elaborating low cholesterol as a risk factor. In this study INH proved highly hepatotoxic, affected 53 (58.24%) patients. INH produces hepatotoxicity by idiosyncratic reaction. Combination of INH with rifampicin and PZA increases the risk of ATT induced hepatotoxicity [9,17]. Rifampicin is relatively an innocent drug in comparison with INH but in this study it caused hepatotoxicity in 32 patients (35.16%). PZA produced hepatotoxicity in 6 (6.95%) patients and its mechanism has been considered to be dose related[20].

## CONCLUSION

ATT-induced hepatotoxicity occurs frequently, usually reversible and rarely fulminant. Malnutrition, low albumin, acetaminophen, female sex, older age, and low serum cholesterol were proved as the risk factors. Since tuberculosis is a common problem in Sindh, special efforts are needed to tackle the drug related complications associated with antituberculosis chemotherapy.

## REFERENCES


1. World Health Organization. Global tuberculosis control: surveillance, planning, financing: WHO report 2008. Geneva 27, Switzerland.
2. Parasarthy, Raghupati, Sharma RG, Janardanam B, Ramachandran P, Santha T, et al. Hepatic toxicity in South Indian patient during treatment of TB with short course regimen containing INH, RMP and PZA. Tubercle Lung Dis 1986; 67:69-108.
3. Koponoff DE, Snider DE Jr, Caras GJ. INH-related hepatitis: a US-public health service cooperative surveillance study. Am Respir Dis 1978; 117(6):991-1001.
4. Garibaldi RA, Drusin RE, Ferebee SH, Gregg MB. INH-associated hepatitis; report of outbreak. Am Rev Respir Dis 1972; 106.
5. Hussain Z, Kar P, Husain SA. Anti-tuberculosis induced hepatitis: risk factors, prevention and management. Indian J Exp Biol 2003;41(11):1226 -32.
6. Choa HJ, Kohb WJ, Ryub YJ, Kia CS, Namc MH, Kima JW, et al. Genetic polymorphism of NAT 2 and CYP 2E1 associated with antitubercuosis drug induced hepatotoxicity in Korean patients with pulmonary tubercuosis. Cell 2007;05:12.
7. Singh J, Arora A, Thakur VS, Pande JN, Tandon RK. Antituberculosis treatement induced hepatotoxicity: role of predictive factors. Postgrad Med J 1995; 71: 359-62.
8. Olson KR Poisoning. In: Tierney LM Jr, Mc-Phee SJ, Papadakis MA, editors. Current medical diagnosis and treatment. 47th ed. New York: McGraw-Hill; 2008.1365-6.
9. Roden DM. Clinical Pharmacology. In: Fauci AS, Braunwald E, Kasper D, Hauser SL, Longo DL, Jameson JL, et al, editors. Harrison's priciples of internal medicine. 17th ed. New York: McGraw-Hill; 2008.35.
10. Tanaogllu K. The management of anti-TB drug-induced hepatotoxicity. The Int Union Against Tuberculosis Lung Disease 2001; 5(1):65-9.
11. Türktaş H, Ünsal M, Tülek N, Örüç O. Hepatotox-

icity of antituberculosis therapy (rifampicin, isoniazid and pyrazinamide) or viral hepatitis. Tubercle Lung Dis 1994; 75:58-60.
12. Combs DL, O'Brien RJ, Geiter LJ. USPHS tuberculosis short course chemotherapy trial 21: Effectiveness, toxicity and acceptability. The report of final results. Ann Intern Med 1990; 112:397-406.
13. Mahmood K, Hussain A, Jairamani KL, Talib A, Abbasi B, Salkeen S. Hepatotoxicity with antituberculosis drugs: the risk factors. Pak J Med Sci 2007; 23(1):33-8.
14. Dorteh S, Askgaard DS. TB chemotherapy: The need for new drugs. Hepatotoxicity caused by the combined action of INH and RMP. Thorax 1995; 60:213-4.
15. Marvin W. Impacts of gender on drug responses. Drug Topics 1998; 591-600.
16. Chang KC, Leung CC, Yew WW, Tam CM. Standard antituberculosis therapy and hepatotoxicity: do dosing schedule matters? Eur Resp J 2007; 29:347-51.
17. Shakya R, Rao BS, Shrestha B. Evaluation of risk factors for anti-tuberculosis drug induced hepatotoxicity in Nepalese population. Ann Pharmacother 2004; 38(6):1074-9.
18. Kishore PV, Palaian S, Ojha P, Shanker PR. Pattern of adverse drug reactions experienced by tuberculosis patients in a tertiary care teaching hospital in Western Nepal. Pak J Pharm Sci 2008; 21(1):51-6.
19. Mehta S. Malnutrition and drugs: clinical implications. Dev Pharmacol Ther 1990; 15(3-4):159-65.
20. Micheal T, Lawrence S, Friedman. Hepatotoxicity of antibiotics and anti fungals: drug hepatotoxicity. Clinics Liv Dis 2003;7(2):381-99.

*AUTHOR AFFILIATION:*

**Dr. Haji Khan Khoharo** *(Corresponding Author)*
Assistant Professor, Department of Medicine.
Muhammad Medical College Hospital
Mirpurkhas, Sindh-Pakistan.
E-mail: drhajikhan786@yahoo.com
drhajikhan786@gmail.com

**Dr. Shuaib Ansari**
Senior Registrar, Department of Medicine
Liaquat University Hospital
Hyderabad/Jamshoro, Sindh-Pakistan.

**Dr. Ali Akber Siddiqui**
Assistant Professor, Department of Medicine.
Isra University Hyderabad, Sindh-Pakistan.

**Dr. Fatima Qureshi**
Medical officer
Muhammad Medical College Hospital
Mirpurkhas, Sindh-Pakistan.