Anti-tuberculosis drugs related hepatotoxicity; incidence, risk factors, pattern of changes in liver enzymes and outcome

*[1]Khalili H., [1]Dashti-Khavidaki S., [2]Rasoolinejad M., [1]Rezaie L., [1]Etminani M.

[1]Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. [2]Department of Infectious diseases, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Background and the purpose of the study: Tuberculosis is a curable disease if diagnosed and treated properly with anti-tuberculosis drugs. These drugs can cause severe adverse reactions including hepatotoxicity.The goal of this study was to evaluate the rate and the time of incidence, pattern of alterations in liver enzyme, risk factors and outcome of anti-tuberculosis drugs induced hepatotoxicity in Iranian Tuberculosis patients.

Method: In a prospective cohort study, 102 patients (68 male, 34 female, mean age 43.21±18 years) with tuberculosis diagnosis were followed during anti-tuberculosis drug treatment course. Drug related hepatotoxicity was defined as increase in serum alanine aminotransfrase or aspartate aminotransfrase greater than three or five times of the upper limit of normal, with or without symptoms of hepatitis, respectively.

Results: anti-tuberculosis induced hepatotoxicity was detected in 32 (31.37%) of the patients. Human immunodeficiency virus and hepatitis C virus infections, concomitant use of hepatotoxic drugs, and abnormal baseline serum alanine aminotransfrase and aspartate aminotransfrase level were risk factors for anti-tuberculosis drugs induced hepatotoxicity.

Conclusion: Anti-tuberculosis drugs induced hepatotoxicity is a major problem in Iranian tuberculosis patients and cause treatment interruption in 31.37% of patients.

Keywords: *Anti-tuberculosis, Adverse drug reactions, Hepatotoxicity, Risk factors*

INTRODUCTION

Approximately one third of the world population infected with *Mycobacterium tuberculosis* and tuberculosis (TB) in one of the main cause of morbidity and mortality in developing countries (1). If diagnosed and treated properly with anti-TB drugs, TB is a curable disease. These drugs can cause severe adverse reactions including hepatotoxicity. Hepatic transaminase elevation without clinical presentation is common and benign episode following anti-TB treatment, but symptomatic hepatotoxicity can be fatal without any intervention (2, 3). From the first line anti-TB drugs, isoniazid, rifampicin and pyrazinamide are potentially hepatotoxic (4, 5).

Based on hepatotoxicity diagnosis criteria and population under study, incidence of anti-TB related hepatotoxicity is reported from 2% to 28% (6). High alcohol intake, older age, pre-existing chronic liver disease, chronic viral infection due to hepatitis B (HBV) and hepatitis C viruses (HCV), human immunodeficiency virus (HIV) infection, advanced TB, Asian ethnicity, female sex, concomitant administration of enzyme-inducers, inappropriate use of drugs and poor nutritional status increase the risk of anti-TB drug induced hepatitis. (3, 6, 7). Hepatotoxicity due to anti-TB drugs has been evaluated as a part of adverse drug reactions (ADR) assessment in previous studies and based on recent literature review, there is not any specific report of this reaction in Iranian TB patients.

The goal of this study was to evaluate the rate, time of incidence, pattern of alteration in liver's enzymes, risk factors and approach and outcome of anti-TB drugs induced hepatotoxicity in Iranian TB patients.

Method

In a prospective cohort study, 102 patients (68 male, 34 female, mean age 43.21±18 years) with TB diagnosis were followed during anti-TB drug treatment course between February 2007 to April 2008. Diagnosis of TB was based on the WHO criteria including; a positive culture for *Mycobacterium tuberculosis* or negative culture associated with clinical and radiological features and response to treatment consistent with TB or histological findings.

Correspondence: khalilih@tums.ac.ir

(8) Study was carried out in infectious disease ward of Imam Hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran. The study protocol was approved by the institutional review board and all patients provided written consent form. Excluding criteria were patients less than 18 years old, and those with history and evidence of liver dysfunction. Also patients with suspected multi-drug resistant (MDR) and extensively drug resistant (XDR) TB were excluded from the study.

Based on WHO recommended standard, treatment for TB in Iran was a regimen of isoniazid, rifampicin, pyrazinamide and ethambutol for initial phase, followed by isoniazid and rifampicin at continuation phase (8).

For all patients involved in the study a complete history and physical examination were taken and patients' demographic characteristics, history of smoking, alcohol drinking, drug abuse, concomitant use of drugs, diseases status, history of viral infections and other treatment information were collected.

Laboratory tests before initiation of anti-TB drugs included; complete and differential blood counts, renal function tests (serum creatinine and blood urea) and serological tests for hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibody (anti-HCV). Liver function tests including alanine aminotransfrase (ALT), aspartate aminotransfrase (AST), alkaline phoaphatase (ALK.P) and bilirubin were performed before initiation of anti-TB drugs and following at 1, 2, 4, 6 and 8 weeks after initiation of treatment. Also Patients were followed clinically during tuberculosis treatment course.

Based on ADR definition of WHO; 'Any noxious or unintended response to a drug which occurs at doses which are used in human normally for prophylaxis, diagnosis or treatment of disease or for modification of physiological function's were considered as ADR (9).

Causality assessment including; definite, probable, possible, unlikely and uncertain was carried out according to WHO criteria (10).

Drug related hepatotoxicity was defined as increase in serum ALT or AST greater than three or five times of the upper limit of normal (ULN), with or without symptoms of hepatitis, respectively (11). The severity of hepatotoxicity was classified according to the WHO Toxicity Classification Standards (12). Based on this definition severity of hepatotoxiciy was considered as follow: mild (ALT or AST < 2.5 times of the ULN), moderate (ALT or AST 2.5–5 times of the ULN), severe (ALT or AST 5-10 times of the ULN) and very severe (ALT or AST >10 times of the ULN). In the case that Alk.P was more than two times of the ULN along with pruritus, jaundice or hyperbilirubinemia, it was considered as cholestatic hepatitis (13).

In patients with diagnosis of drug induced hepatitis, all the anti-TB drugs were discontinued and patients were followed by both clinical and biochemical parameters for signs and symptoms of drug induced hepatotoxicity. When all signs and symptoms of drug induced hepatotoxicity disappeared and the liver function tests decreased to near of the normal range, treatment was attempted sequentially based on the following hospital protocol. Ethambutol was started with full dose (15 mg/kg) plus rifampin 150 mg at the first day, 300 mg at the second day, 450 mg at the third day and then 600 mg/daily. If Rifampin was tolerable, at the fourth day isoniazid was started as follows; isoniazid 50 mg at the first day, 100 mg at the second day, 150 mg at third day and then 300 mg/daily. If patient tolerated, then pyrazinamide started as 500mg at the first day, 1000 mg at the second day and then continued at doses which was determined on the basis of patient's body weight.

Statistical analyses

SPSS version 11.5 was used for analysis of data. Chi-square, Fishers exact tests and multivariate analysis were used to test for the level of significance. Multiple regression analysis was used to evaluate the effect of different confounding factors. Hepatotoxicity was the dependant variables whereas age, sex, HBsAg, concomitant drug intake, HIV status and anti- HCV antibody were the independent variables. OR and P-values were used to find the significant risk factors. Variables with $p < 0.05$ were considered potential predictors of drug induced hepatotoxicity.

RESULTS

Basic characteristic of the patients is shown in table 1. Sixty eight (66.66%) of patients were male and 40 patients (39.21%) were over 35 years old. Co-morbidities in patients under study were hypertension, hyperlipidemia, gastrointestinal upset, diabetes mellitus and rheumatoid arthritis. Concomitant use of other hepatotoxic drugs (ranitidine, methotrexate, nevirapine, methyldopa, cotrimoxazole, lovastatin and pioglitazone) was recorded in 8 (6.66%) of patients.

HIV, HBV and HCV co-infections were detectedin in the 32 (31.37%), 8 (7.84%) and 28 (27.45%) patients respectively. Forty seven (46.07%) of patients had history of drug abuse of which 32 (31.37%) were injection drug users. At the habitual history 49 (48.03%) of patients were smoker and 10 (9.80%) of them had history of occasional alcohol consumption.

Anti-TB drugs induced hepatotoxicity was detected in 32 (31.37%) of patients. Frequency of this reaction based on degree of severity is shown in table 2.

ALT was raised more than 5 times of ULN in 14 (43.75 %) of hepatotoxic patients and GI symptoms plus 3-5×ULN elevation of ALT were detected in 18

Table 1. Demographic Characteristics of the patients.

Parameter	Number (%) of patients
Total number of patients	102
Sex	Male = 68 (66.66), Female = 34 (33.34)
Age	43.21 ± 18.27
Status of viral infection	
HIV [1]	32 (31.37)
HCV[2]	28 (27.45)
HBV [3]	8 (7.84)
History of smoking	49 (48.03)
History of alcohol consumption	10 (9.80)
History of drug abuse	47 (46.07)
Co- morbidity	
Diabetes	7 (6.86)
Gastrointestinal Upset	8 (6.66)
Cardiovascular diseases	14 (13.72)
Rheumatologic diseases	3 (2.94)
Concomitant hepatotoxic drugs	8 (6.66)

[1]HIV: Human Immunodeficiency Virus, [2]HCV: Hepatitis C Virus, [3]HBV: Hepatitis B Virus

(56.25%) of these patients. The mean time which was elapsed between starting of anti-TB drugs and elevation of ALT was 14.17 ± 9.67 days.

After detection of liver injury, all anti-TB drugs were stopped and most patients' ALT serum levels returned to less than 2× ULN after 7.5 ± 4.6 days. At this time, anti-TB drugs were re-administered based on the hospital protocol. After re-starting of anti-TB drugs, liver enzymes were raised in 13 patients (1 patient after starting RIF, 3 patients after addition of INH and 9 patients after including PZA), thus the overall hepatotoxicity of RIF, INH and PZA were 1%, 3% and 9% respectively. In these patients the related drug was discontinued and proper drug was replaced or duration of treatment was prolonged. Other patients tolerated the regimen after re-exposure.

After assessment of risk factors for hepatotoxicity, HIV and HCV co-infection, concomitant use of hepatotoxic drugs, and abnormal baseline serum ALT and AST levels were significant (Table 3).

DISCUSSION

Anti-TB drugs induced hepatotoxiciy is a serious problem and main cause of treatment interruption during TB treatment course. It is reported that 1-28% of TB patients experience drug related hepatotoxicity following treatment (6, 14).

Prevalence of anti-TB induced hepatotoxicity in Iran is reported from 16.06 to 27.70 percent in previous studies (15, 16). In this study 31.37% of the patients showed anti-TB related hepatotoxicity.

Table 2. frequency and severity of anti-tuberculosis drugs induced hepatotoxicity

Severity of Hepatotoxicity	Frequency (%)
Moderate	19 (18.7)
Severe	8 (7.8)
Very Severe	5 (4.9)

Higher prevalence of anti-TB induced hepatotoxicity in Iran may be related to several factors such as race, metabolic pathway polymorphism, malnutrition, undiagnosed baseline liver diseases, and severity of TB. The hospital of this study is a tertiary referral hospital and complicated patients usually were referred to this centre. In the previous studies, hepatotoxicity of anti-TB drugs was evaluated and as a part of study goals and adverse reactions to all antibiotics or anti-TB drugs were reported (15, 16). In the present study, we focused on anti-TB closely as a part of clinical pharmacy services and pharmaceutical care in infectious disease ward in the hospital.

In the present study pattern of alteration of liver enzymes was evaluated. The mean time elapsed between starting of anti-TB drugs until elevation of ALT was comparable with the previous report (15). Rifampin is reported to be less hepatotoxic than other anti-TB drugs but it may increases the incidence of hepatotoxicity of other drugs, especially isoniazid (17). In the present study only 1% of the patients showed hepatotoxicity symptoms after re-administration of rifampin.

Pyraziamide have been reported to cause more hepatotoxicity than other anti-TB drugs (18, 19). In the present study also the most important cause of enzyme elevation after drug re-challenge was pyrazinamide and it occurred in 9% of patients.

Documented risk factors in the present study were HIV infection, HCV infection, concomitant use of hepatotoxic drugs and abnormal baseline serum ALT or AST serum level.

Viral hepatitis and HIV infection increase risk of drug associated hepatitis up to 3-5 times (20). Fourteen fold increases in the risk of anti-TB hepatotoxicity has been reported in HIV and HCV co-infected patients (11).

Although HBV infection has been reported as a risk factor in some studies (3, 21), there was no correlation between HBV infection and anti-TB drugs hepatotoxicity in this study that may be related to limited number of HBV infected patients who participated in the study.

Abnormal baseline liver enzymes increased incidence of anti-TB drugs hepatotoxicity in the present study which was consistent with another report (19).

Although it has been reported that advanced age can be a risk factor for liver injury following TB drug treatment (18, 21), in the present study such

Table 3. Assessment of risk factors for hepatotoxicity.

Risk factor	OR[1]	95% CI[2]	p-value
Male gender	1.67	0.65-4.24	0.35
Age > 35y/o	1.85	0.91-2.25	0.26
Smoking	1.67	0.66-4.18	0.19
Alcohol abuse	1.05	0.36-3.03	0.56
HIV[3] infection	3.5	1.31-9.32	0.01
HCV[4] infection	2.93	1.07-7.96	0.04
HBV[5] infection	0.46	0.04-4.35	0.65
Concomitant hepatotoxic drugs	1.30	1.11-2.36	0.03
Diabetes	0.96	0.16-5.62	0.66
Baseline ALT[6] > 2×ULN[7]	5.87	1.22-10.11	0.02
Baseline ALS[8] > 2×ULN	4.29	1.65-8.65	0.01
Baseline Alk.P[9] > 2×ULN	0.85	0.32-2.09	0.81

[1]OR: Odds Ratio, [2] CI: Confidence Interval, [3]HIV: Human Immunodeficiency Virus, [4]HCV: Hepatitis C Virus, [5]HBV: Hepatitis B Virus, [6]ALT: Alanine aminotransfrase, [7]ULN: Upper Limit of Normal, [8]AST: Aspartate aminotransfrase, [9]ALK.P: Alkaline phoaphatase

correlation was not found. Also in previous studies, advance age was not a risk factor for anti-TB drugs induced hepatotoxicity in Iranian TB patients (15, 16).

Concomitant use of hepatotoxic drugs (ranitidine, methotrexate, methyldopa, cotrimoxazole, statins and pioglitazone) was risk factor for anti-TB induced liver injury in patients of this study. Additive liver injury due concomitant use of hepatotoxic drugs has also been reported (21). Anticonvulsants and acetaminophen have been reported to increase the incidence of anti-TB hepatotoxicity (22).

Alcoholic patients are more vulnerable to hepatotoxicity of drugs (3, 18, 22) but in this study it was not a risk factor. Most of alcoholic patient use to drink alcohol as a refreshment habit and can not be included in the alcoholic definition.

Detoxification of drugs and metabolites are related to activities of liver enzymes. In different populations, polymorphism of these enzymes can cause variation of anti-TB hepatotoxicity (23). Pharmacogenetic study may be recommended for drug treatment individualization, especially for
anti-TB drugs.

ADR including hepatotoxicity can be one of the main reasons for poor adherence with Anti-TB treatment in tuberculosis patients (24). In the present study anti-TB drugs induced hepatotoxicity was main cause of TB treatment interruption (31.37%) and change in treatment regimen (13%).

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