

# Drug-induced Hepatitis (Abundance and Outcome During Course of Tuberculosis Treatment): Seven-year Study on 324 Patients with Positive Sputum in Iran

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## ABSTRACT

**Background:** Hepatotoxicity is a major concern during tuberculosis (TB) drug therapy. Its prevalence ranges from 1%-4% in developed countries to 11.5% in developing countries, and is even higher in countries such as India. Disease mortality is 5%, but can be prevented by early detection. This study reveals the prevalence and outcome of drug-induced hepatitis (DIH) in positive sputum TB patients taking anti-TB drug therapy in Qazvin Province, Iran.

**Materials and Methods:** This observational, descriptive, retrospective cross-sectional study was done on 324 patients (newly diagnosed cases) with positive sputum TB who took anti-TB drugs as the six months classic regimen Direct Observed Treatment Short course (DOTS) method of isoniazide + rifampin + pyrazinamide + ethambutol or streptomycin for two months followed by isoniazide + rifampin for four months, from 2004-2010.

**Results :** The mean age of the cases was 42±12.1 years (mean±SD). A total of 194 cases (60%) were female and the remaining were male. DIH was seen in 16 cases (4.9%). The mean age of affected cases was 52 years. Liver enzymes had begun to rise 13-45 days after drug therapy (mean=25.25), the peak of the enzyme rise was 287-605 i.u. The enzyme level returned to normal after 14-43 days (mean=23.45) after discontinuation of the drugs. There was no mortality.

**Conclusion :** The prevalence of DIH in our study was 4.9%. Although it was seen more in females over 50, no statistically significant relations were found between DIH and sex or age of the patients. With baseline and bi-weekly liver enzyme checks and rapid drug discontinuation in raised cases, mortality was not observed.

**Keywords:** Drug-induced hepatitis; Tuberculosis; Positive sputum; Outcome

*Govareh/ Vol. 16, No.2, Summer 2011; 134-138*

## INTRODUCTION

Drug-induced hepatitis (DIH) is one of the potential life-threatening adverse effects of first-line anti-TB drugs. These drug side effects should be diagnosed earlier and managed as soon as possible. Without

attention, the risk of mortality can increase up to 5%(1,2).The prevalence of DIH has been reported from 1% to 3-4%, and even as high as 11%(3-6).

Anti-TB drugs may impair hepatic function and lead to clinical manifestations or impairment in liver function tests (liver enzymes and bilirubin). Most cases of anti-TB drug hepatotoxicities arise early in the course of treatment(7 ).Although DIH is dose-related, it is more commonly idiosyncratic(8).

A variety of factors may contribute to DIH after anti-TB drugs including age, female sex, malnutrition, low body mass index (BMI), chronic alcoholism, chronic liver diseases, hypoalbuminemia, hypergammaglobulinemia, positive HBS-Ag, anti-TB drug overdose, acetylation status, and HIV infection(7, 9-12).

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Received : 10 Aug. 2011

Edited : 15 Sep. 2011

Accepted : 16 Sep. 2011

The diagnosis of DIH can be difficult. There is no gold standard and no specific serum biomarker or characteristic histologic feature that reliably identifies a drug as the cause of toxicity. Features suggestive of drug toxicity include a lack of illness prior to ingesting the drug, no underlying liver disease, clinical illness or biochemical abnormalities that develop after beginning the drug, and improvement after the drug is withdrawn(13).

With an early diagnosis and drug discontinuation, patients can complete treatment after liver enzyme normalization. A delay in diagnosis may lead to acute hepatic failure and even death.

DIH prevalence varies in different geographic areas, possibly ethnic races, and it is a main cause of mortality in TB patients. Unfortunately there are few data about the hepatotoxicity of anti-TB drugs from Iran. This study was conducted to determine the incidence and prognosis of DIH in Qazvin Bouali Hospital.

## MATERIALS AND METHODS

This observational, descriptive, retrospective study was done on 324 patients in Qazvin Bouali Hospital from 2004–2010.

Diagnosis of sputum positive TB was made according to the WHO guidelines(14). Cases were included in the study if they had a normal liver enzyme and were treated according to WHO protocol. The following cases were excluded from the study:

- 1-Abnormality in the level of liver enzymes at the start of anti-TB drug therapy
- 2-History of chronic liver diseases or cirrhosis
- 3-History of alcohol or drug abuse
- 4-HBS-Ag positive, HCV-Ab positive, or HIV positive
- 5-Concurrent use of other hepatotoxic drugs
- 6-Non-Iranian patients
- 7-Non-classic treatment methods
- 8-Patients with treatment failure
- 9-Patients with multi-drug resistant TB (MDR TB)

The length of treatment and drug doses were based on WHO recommendations, and included isoniazide, rifampin, pyrazinamide, and ethambutol or streptomycin for two months followed by isoniazide and rifampin for four months(14). All patients were treated according to the Direct Observed Treatment Short course (DOTS) and patients were trained about the adverse drug effects and visited by a physician one month after starting the drugs. The following visits

were done monthly unless an adverse effect occurred. If the patients developed symptoms of hepatitis such as nausea, vomiting, abdominal pain or jaundice, or an ALT greater than 5-fold, were recognized as DIH. All relevant data including sex, age, duration of anti-TB treatment, time of hepatitis onset, level of ALT, time of normalization of liver tests, and the final outcome were taken from the university hospital files between 2004-2010 in Qazvin (central Iran). Our descriptive, retrospective cross-sectional study was done with Qazvin University of Medical Sciences Ethics Committee permission. Data were analyzed by SPSS software(15).

## RESULTS

During the study period, 324 cases with a diagnosis of sputum positive TB underwent anti-TB drug therapy. 194 (60%) were females and the remaining were males. Mean age of the patients was  $42 \pm 12.1$  (mean  $\pm$  SD); in females it was  $49 \pm 16.3$  and in males  $41 \pm 11.2$ . Among the patients, 16 cases (4.9%) suffered from DIH, which included 10 females and 6 males. The rate of DIH among female patients was 5.15% and in male patients 4.61%. Mean age of affected cases was 52 years. The rate of DIH among patients more than 50 years (9 cases) was 7.27%, while the rate was 3.46% in patients with an age of less than 50 years. Clinical symptoms of hepatitis (nausea, vomiting, abdominal pain or jaundice) were reported in five cases. The mean time between onset of drug therapy and diagnosis of hepatitis was 25.25 days (range: 13-45 days). ALT was elevated at 287-605 I.U, it returned to normal with a mean time of 23.45 days (range: 14-43 days). ALT returned to normal in all patients after cessation of anti-TB drugs. Afterwards, the drug regimen was restarted and completed successfully. No mortality was reported. Detailed data of each patient are shown in Table 2.

## DISCUSSION

In this study we have reported DIH in 16 cases (4.9%). Many different reports are available about the prevalence of anti-TB drug hepatotoxicity. In a review, Tostman and his colleagues concluded its prevalence to be 2%-28%(15). Daphne reported its prevalence as 3% in 430 patients who underwent treatment for active TB in Canada(16). Fernandez-Villar and his colleagues have found the prevalence to be 18.2% in patients with risk factors of old age, chronic hep-

**Table 1: Demographic characteristics of patients.**

Variables			<i>p</i> - value
Sex	Male (6)	Female (10)	<i>p</i> = 0.96
Age	<50 (7)	>50 (9)	<i>p</i> > 0.5

**Table 2: Detailed data of patients affected with anti-TB drug induced hepatitis.**

Patient code	Sex	Age	ALT level at time of diagnosis (I.U)	Time (days) of diagnosis (after starting therapy)	Time (days) of ALT normalization (after diagnosis)	
1	M	42	375	16	21	alleviated
2	M	53	346	25	20	alleviated
3	M	48	402	24	26	alleviated
4	M	65	524	26	27	alleviated
5	M	68	408	18	22	alleviated
6	M	35	384	35	17	alleviated
7	F	42	375	25	21	alleviated
8	F	65	482	18	27	alleviated
9	F	45	395	19	19	alleviated
10	F	52	525	42	26	alleviated
11	F	72	297	35	17	alleviated
12	F	48	605	45	43	alleviated
13	F	58	367	19	18	alleviated
14	F	72	287	13	17	alleviated
15	F	68	468	28	40	alleviated
16	F	36	329	16	14	alleviated

atitis B or C, severe TB, malnutrition, and alcoholism; and 5.8% in patients without such risk factors in Europe(17). The prevalence was 5.6% in a study in China, which was seen mainly during the first nine weeks of treatment(18). Various reports have shown a prevalence of 3%-10% in Great Britain,(19,20) 11.5% in India,(6) 9.7% in Malaysia,(21) 15% in Egypt,(22) 19.76% in Pakistan(23) 8% in Ethiopia,(24 ) and 13% in Iran(25).

The difference in reported figures may be due to different definitions of drug hepatitis and a difference in the studied populations(26). Our figure (4.9%) is close to that of European countries, and much less than developing countries such as India, Ethiopia, Malaysia, Singapore, Egypt and Pakistan. It may be due to race or better monitoring in developing countries.

In many similar studies anti-TB drug hepatotoxicity has been noted as more common in females(10, 22, 23, 27, 28). The same findings are seen in our study, but the difference was not statistically significant ( $p = 0.96$ ).

Various authors have shown the time of incidence of anti-TB drug hepatotoxicity as 12-60 days after starting treatment(18,19,22,23, 25). In our study we found it to be 13-45 days, and no cases were seen after the second month. The mean time was equivalent to similar studies(7, 22, 24, 25). Clinical and laboratory monitoring of symptoms and signs of hepatitis in patients has significant importance, especially in the first two months after starting drug therapy.

The follow up recommendations are different in different countries. In Spain clinical follow up is based

on risk factors and lab screens are done during the second and fourth weeks of treatment and after the second and fourth months. In the USA, monthly follows are recommended for all patients and a preliminary LFT and intervallic laboratory screen for high-risk patients. In Great Britain a weekly check for the first two weeks and examinations every two weeks for the first two months is suggested(26).

Risk factors of anti-TB drug hepatotoxicity (such as HIV, hepatitis B and C, malnutrition, and chronic liver diseases) have inconsistent prevalence in various societies. More controls are needed for those populations with a higher prevalence.

In our study if the ALT rise was 3-5 fold, INH was stopped and monitoring increased. All drugs were stopped if the rise was more than 5-fold; ALT level was then checked weekly until normalization. Afterwards, the drugs were restarted at low doses and then increased gradually. In this way, we could manage

hepatotoxicity and successfully finish anti-TB treatment.

Byoung has proposed that the drugs can be restarted safely with a standard classic regimen after liver enzyme normalization, even in HBS-positive patients(27).

The mean time for normalization of ALT was 23.4 days (14-43 days) in the present study. The similar figure was 10.26 days in another study(25).

No mortality was found in the present study; however there are some reports of mortality in a few studies due to severe hepatotoxicity and acute liver failure(17, 19).

With a baseline and liver enzyme checks every two weeks, and rapid drug discontinuation in raised cases, we did not observe any mortality in this study. However, similar studies are needed to confirm our findings and conclusions.

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