Evaluation of Prophylactic Role of Liver Supports in Patients Receiving Anti Tuberculous Therapy

M M SHAIKH M N IMRAN
Institute of Chest Medicine and Tuberculosis, King Edward Medical College, Mayo Hospital Lahore
Correspondence to Dr. Muddassir Muhammad Shaikh, E.mail: muddassirmuhammad@hotmail.com

Study objective: To study the possible role of liver supports in prevention (prophylaxis) of hepatitis/jaundice in patients receiving antituberculous therapy (ATT). **Introduction:** Drug induced hepatotoxicity is a major problem arising in patients receiving antituberculous therapy and has been well documented. There are many liver supports available in the pharmaceutical market like silymerin and ornithine aspartate etc. which claim to have a potent effect in reducing the hepatotoxicity induced by ATT or other drugs. This study was conducted to see whether they have any true fact in the claim of prevention of hepatotoxicity induced by ATT. **Materials and methods:** The study was conducted from 01-06-03 to 30-06-04. A total of two hundred and four (204) patients suffering with tuberculosis were enrolled. These patients were divided into two equal groups (randomly). Group A was started standard first line antituberculous therapy without liver support. Group B received liver support in some form. The patients in group B were further divided into 3 sub-groups. Two subgroups received one of the two liver supports and the third subgroup received both. These patients were followed weekly for eight weeks (by measuring liver function tests) for any evidence of hepatotoxicity. Hepatotoxicity was defined as serum bilirubin more than 1.0 mg/dL and/or liver enzymes greater than four times the base-line value. **Results:** Among 204 patients, 16 patients developed hepatotoxicity. Out of which 6 belonged to group A (with out liver support), 4 to group B-1 (silymerin), 4 to group B-2 (ornithine), while 2 to group B-3. **Conclusion:** We conclude that there is no statistically significant difference (p value >.o5) in the incidence of hepatitis in both groups.
Key words: Anti tuberculous therapy, hepatotoxicity, liver supports

Tuberculosis is a chronic granulomatous infection caused by "Mycobacterium Tuberculosis". It can affect any organ of the body but most commonly involves the lungs. It is one of the commonest chronic disease, especially common in third world countries although it is also getting resurgence in western world and USA because of HIV infection. 98% of annual deaths from TB and 95 % of cases of tuberculosis are prevailing in third world. According to WHO the incidence of tuberculosis in Pakistan is estimated to be 177/100000 annually, although the prevalence is much higher than that; however the exact magnitude of problem in Pakistan is unknown[1].

After making the diagnosis of tuberculosis patient is administered first line (four or five) antituberculous drugs including rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin. Drug induced hepatotoxicity is a major problem arising in patients receiving these drugs has been well documented. [2]The over all incidence of hepatotoxicity is about 2%. Among these first line antituberculous drugs; pyrazinamide, rifampicin and isoniazid are considered to be hepatotoxic.

There are many liver supports (hepatoprotective agents) available in the pharmaceutical market like silymerin and ornithine aspartate etc. which claim to have a potent effect in reducing the hepatotoxicity induced by ATT or other means. This study was conducted to see whether they have any true fact in the claim of prevention of hepatotoxicity induced by ATT.

Materials and methods:

Study design: It was a unicentered, single blind, randomized, prospective, investigator initiated, consent based study. The study was conducted from 01-06-03 to 30-06-04. A total of two hundred and four (204) patients were enrolled suffering with pulmonary and extra-pulmonary tuberculosis of any organ at institute of chest medicine KEMC, Mayo hospital Lahore; both from in patient (144) and out patient (60) department. These patients were divided into two equal groups (randomly). In group A, 102 patients were enrolled while in group B, 102 patients were equally divided into three sub groups each having 34 patients. Group A was started standard first line antituberculous therapy without liver support. Group B received liver support in some form. It was further divided into three equal subgroups (randomly). In group B-1 patients were started with standard antituberculous therapy with tablet containing silymerin 200 mg twice a day. Group B-2 was started antituberculous therapy, with syrup containing ornithine aspartate 300 mg, nicotinamide 24 mg and riboflavin-5 phosphate sodium 76 mg per 5 ml. Group B-3 was started with standard antituberculous therapy with both of these two drugs.

Table 1: Patients enrolled (n-204)

Group A	Group B	B-1	B-2	B-3
102	34	34	34	

Inclusion criteria

Tuberculosis of any organ & any sex
Age greater than 12 years
No previous history of ATT intake
Normal base line level of liver enzymes (SGOT less than 40 and SGPT less than 45) and base line bilirubin of less than 1.0 mg/dL.

Markers for hepatitis B and C negative
No evidence of chronic liver disease (liver cirrhosis) on ultrasound

Follow up
These patients were followed weekly for eight weeks (by measuring liver function tests) for any evidence of hepatotoxicity. Hepatotoxicity was defined as serum bilirubin more than 1.0 mg/dL and/or liver enzymes (transaminases) greater than four times the base lines value.

Results:
Among 204 patients 16 patients developed hepatotoxicity. Out of which 6 belonged to group A (without liver support), 4 to group B-1 (silymerin), 4 to group B-2 (ornithine), while 2 to group B-3. Half of the patients out of 16 patients developed hepatotoxicity in first week out of which 4 belonged to group A and 4 belonged to group B-2 and group B-3 (2 in each group). 25 % developed jaundice in second week out of which 2 belonged to group A and 2 belonged to group B-2.12.5 % developed jaundice in third week, both of these patients belonged to group B-1. Remaining 12.5 % developed jaundice in fourth week which again belonged to group B-1.

Table 2: Results showing Hepatotoxicity in each group(P-value-0.317)

	Group A	Group B			
		B-1	B-2	B-3	total
Developed Hepatotoxicity	6	4	4	2	10
Did not develop Hepatotoxicity	96	30	30	32	92
Total	102	102			

Discussion:
As mentioned earlier tuberculosis is a very common disease in third world. Even though the overall incidence of hepatotoxicity in patients receiving antituberculous therapy is only 2% but considering the great number of patients who are receiving it, this presents a significant problem. [3]This hepatotoxicity ranges in severity from asymptomatic elevation of serum transaminases to clinical symptoms and hepatic failure. Among antituberculous drugs isoniazid, rifampicin and pyrazinamide are known for their hepatotoxic potential[4].

Even thought the exact mechanism of hepatotoxicity caused by these agents in not known but still there are two main mechanisms that are being recognized; (1) Direct toxicity: It occurs with predictable regularity in individuals exposed to offending agent and is dose-dependent. (2) Idiosyncratic toxicity: Occurrence of hepatitis is usually infrequent and unpredictable and is not dose-dependent[5]. Through these mechanisms these hepatotoxic drugs may cause either acute hepatic injury (e.g. hepatocellular necrosis, cholestatic jaundice, hepatocanalicular jaundice, and hypersensitivity type of injury) or chronic active hepatitis. Even though isoniazid is known to cause hypersensitivity type of reaction and chronic active hepatitis, rifampicin is known to cause cholestatic jaundice, and pyrazinamide chronic hepatitis, however there is variable histological presentation will all of these drugs[6].

Isoniazid hepatotoxicity is the commonest of all antituberculous therapy induced hepatotoxicity. Approximately 10-20% of adult patients receiving isoniazid develop elevation of serum transaminases 1-3 times the normal level during the first 2 months of therapy. About 10% of patients who develop mild transaminase elevations (1-2% of all those treated), progress to severe hepatitis. [7,8]Rifampicin causes hepatotoxicity in 1-5 % of patients and pyrazinamide in 1-2 % of patients.

Before start of treatment with these drugs all patients should have base-line liver function tests and viral markers to exclude preexisting chronic liver disease. Symptoms are not a reliable indicator because they may not develop until after potentially lethal damage has occurred[9]. Patients should have two weekly monitoring of liver transaminases initially in the first two month and be tested monthly thereafter[9].

In those who show less then 3 fold increase in the liver transaminases, the monitoring should be made more frequent (twice weekly); [10]If patient is asymptomatic cautious administration of antituberculous drugs can be continued. Patients with elevations of the serum transaminases greater than 3 times the normal level should be evaluated by a hepatologist to carefully consider all possible causes of hepatitis. Transaminase elevations greater than 4-fold higher than normal should prompt discontinuation of drugs.

There are many preparations available which are presumed to have beneficial effects in prevention of hepatotoxicity by these agents, however their exact mechanism of action and precise role has not been identified in large clinical trials and their use is justified mostly as evidence based medicine. Large double blind clinical trials are necessary to establish their role in prevention of antituberculous drugs induced jaundice.

Conclusion:
We conclude that there is no statistically significant difference (p-Value=0.317, i.e. >0.05) in the incidence of hepatitis in both groups and the prophylactic role of liver supports in patients receiving antituberculous therapy needs further evaluation.

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