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STUDY ON THE HEPATOTOXICITY OF ANTI-TUBERCULOSIS DRUGS IN 190 PATIENTS WITH PULMONARY AND EXTRAPULMONARY TUBERCULOSIS

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ABSTRACT

Tuberculosis is one of the oldest diseases that affects humans. The cause of this disease is *Mycobacterium tuberculosis*. This disease affects approximately 8.8 million people worldwide and led to over 3 million deaths in 1995.

95% of those affected and 98% of deaths occurred in developing countries. Hepatic reactions constitute a major proportion of drug reactions to antituberculosis drugs being reported in 4% of cases treated with rifampin/isoniazid and pyrazinamide in the USA and 8-50% in India and developing countries.

For the purpose of identifying the hepatotoxicity of anti-tuberculous drugs, this study was performed in hospitals affiliated to Shahid Beheshti University in Tehran during 1994 to 1997.

The current descriptive study was performed on hospitalized patients diagnosed as having active tuberculosis.

History was taken from all the patients and clinical signs were recorded. Three sputum samples for mycobacterial acid fast stain examination and cultures (three consecutive days) were sent to Pasteur Institute. Liver function tests (AST, ALT, alkaline phosphatase, bilirubin, PT) were performed before treatment and repeated weekly for two weeks then two weekly for the first two months and then monthly until the end of treatment.

From a total of 262 patients during the study, 190 patients were studied. 51% were male and the rest were female.

The lowest rate of TB was in the age group less than 5 and the most frequent rate of TB was in the 56-65 years age group. 107 patients (56.2%) had active pulmonary tuberculosis and 43.7% had extra-pulmonary TB. 44.2% had positive smear sputum, 22.1% had positive biopsy, and 33.6% were diagnosed based on clinical findings, x-rays and other paraclinical tests. 25.7% of patients had increased ALT and AST following the treatment, and in 4.7% of cases the increase was 4-5 times normal and in

3.6% 5 times normal, 8.4% had increase in bilirubin and 6.8% had increase in bilirubin associated with increase in ALT and AST, 8.4% had increased alkaline phosphatase and 7.6% had disturbance in PT.

Considering that 25.7% of the patients had increased levels of liver enzymes and in 3.6% of them the increased level exceeded 5 times that of normal and also 6 cases of 7 were over 35 years old, therefore, anti-tuberculosis drug consumption, must be considered more seriously in patients over the age of 35.

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Keywords: Tuberculosis, liver enzyme, ALT, AST, Bilirubin, Isoniazid (INH), Rifampin (RMP), Pyrazinamide (PZA).

INTRODUCTION

Tuberculosis is one of the oldest diseases that affects humans. The World Health Organization reports that there were 3.8 million new cases of the disease in the beginning of 1990 and 90% of these occurred in developing countries. The estimate for 1995 was 8.8 million cases and 95% of them occurred in developing countries.[1,2]

The drugs used in the treatment of tuberculosis are classified into first and second line. The first line includes isoniazid (INH), rifampin (RMP), ethambutol (ETB), streptomycin, and pyrazinamide (PZA). The second line of treatment is for those patients who are resistant to treatment by first line drugs and include kanamycin, capreomycin, ethionamide, cycloserine, PAS, and quinolone.

Anti-tuberculosis drugs have various side effects. The most significant of these effects is liver complications such as liver dysfunction and/or symptomatic hepatitis.[9,13,21] Liver dysfunction is defined as an increase in ALT and AST levels to 1.5 times the upper limit of normal and symptomatic hepatitis is defined as the presence of malaise, nausea, vomiting, lethargy and/or right upper quadrant discomfort together with the presence of liver dysfunction.[1,2,4,21]

The hepatitis due to INH is observed in 0.3% of people under the age of 35, in 1.2% under 49, and in 2.3% of patients over the age of 50.[1,2,7,14] When INH and RMP are used together the rate of hepatitis increases fourfold[2,7,9,14] and in 10-15% a temporary increase in liver enzymes is observed 4-8 weeks following treatment by INH.[2,10,15] The increase in liver enzymes with RMP is observed in 5-10% but hepatitis occurs in 0.15% - 0.43% and when INH, RMP and PZA are used together the hepatitis rate increases to 2.5%.[2,3,7,13,21] Fatal hepatitis with INH, RMP, and PZA also has been reported (6-12%).[14,17,18]

When monitoring AST and ALT levels before and after treatment, when the increase is 3-5 times greater than normal, INH, RMP and PZA must be stopped and if AST and ALT returns to normal treatment should be resumed and if clinical signs of hepatitis recur the drug must be discontinued and substitution drugs must be used.[3,7,10,11,14,15] Hepatitis occurs more in older patients, people who suffer from liver failure and those using alcohol.[1,2,17]

Since administration of INH, RMP and PZA is now recommended for all cases of tuberculosis, and considering drug complications especially hepatitis associated with it which can lead to death, this study was performed to determine the hepatotoxicity of anti-tuberculosis drugs.

MATERIAL AND METHODS

This was a descriptive study performed prospectively from 1994 to 1997 on hospitalized patients diagnosed as having tuberculosis in Hospitals affiliated to Shahid Beheshti University of Medical Sciences. During this 3 years of study, 262 patients were diagnosed as tuberculosis patients. Complete history was taken, clinical examination was performed and from each patient three sputum samples for Mycobacterial acid fast stain examination and cultures (three consecutive days) were sent to Pasteur Institute for identification of tuberculosis and liver function tests i.e. AST, ALT, bilirubin, PT, and alkaline phosphatase were done prior to treatment and repeated weekly for two weeks then two-weekly for the first two months and then monthly until the end of treatment. The method of diagnosing the patients was based on identifying the organism in sputum smear or sputum culture and/or positive culture of other discharges and/or samples or biopsies, and observing granulomas and/or clinical evidence together with abnormal chest radiography and ruling out other diseases. Strong predictors of active disease included upper-zone disease on the chest radiograph, fever, night sweats and weight loss. Patients entered the study with normal pretreatment liver function tests (AST, ALT, bilirubin, alkaline phosphatase) and with no evidence of cardiac, renal and liver disease such as cirrhosis, hepatitis A, B, or C, and patients with known chronic illnesses such as cirrhosis of the liver, chronic hepatitis, renal or cardiac disease, acute viral hepatitis A, B, or C and patients with increased

liver function tests (AST, ALT, bilirubin, alkaline phosphatase) before treatment were excluded from the study.

Drug regimens

Treatment with four drugs (standard regimen) was started as: rifampin 10-20 mg/kg daily in children (max 600 mg), adults 600 mg daily, isoniazid, adults 300 mg daily, children 5-10 mg/kg (max 300 mg) daily, pyrazinamide 20-30 mg/kg daily (max 1.5-2g), and ethambutol 15-25 mg/kg daily in children, adults 15 mg/kg daily, or streptomycin adults 1 g daily, children 15 mg/kg daily IM.

In cases which drug complications occurred such as hepatitis with symptoms or rise in AST, ALT, or bilirubin 3-5 times normal, appropriate measures such as reducing the dose or temporary discontinuation and restarting the medication after liver function tests had returned to normal or complete discontinuation and substituting with another drug were taken.

Criteria for diagnosing hepatitis included either jaundice, elevated AST, ALT, bilirubin, or clinical manifestations of hepatitis in conjunction with AST, ALT levels exceeding 100 units/dL.

RESULTS

From 262 patients, 72 patients with known chronic illness such as cirrhosis of the liver, renal or cardiac diseases, acute viral hepatitis (A, B, or C) and/or with elevated AST, ALT, bilirubin, or alkaline phosphatase before treatment were excluded from the study. 190 patients, 97 (51%) male and 93 (49%) female entered the study. The age distribution showed that the least frequent rate of disease was for the less than 5 years age group with 4 cases (2.1%). And the age group 56-65 showed the highest rate of the disease with 40 cases (21%) (Table I).

107 patients (56.2%) suffered from pulmonary tuberculosis and 83 patients (43.7%) had extra-pulmonary tuberculosis.

The most important clinical sign of pulmonary tuberculosis included fever in 88 patients (82%), cough and sputum in 67 patients (62.5%), night sweats in 21 patients (20%), chest pain and dyspnea in 17 patients (16%), and bloody sputum in 12 patients (11.2%).

Table I: Distribution of 190 patients with tuberculosis according to age in Hospitals of Shahid Beheshti University in Tehran.

Age (year)	Number	Percent
0-5	4	2.1
6-15	6	3.15
16-25	26	13.7
26-35	30	15.8
36-45	25	13.15
46-55	24	12.6
56-65	40	21
>65	35	18.2

From a total of 190 patients, 84 cases (44.2%) had positive culture or smear and 42 patients (22.1%) had positive biopsy and granuloma characteristics of TB. And 64 patients (33.6%) were diagnosed based on clinical and paraclinical evidence and abnormal chest radiography.

From the 190 patients, 49 patients (25.7%) showed increased liver enzymes. Most of these patients showed increase in the first month after the treatment.

In 141 patients (74.2%), the enzymes were normal, in 33 patients (17.3%), the enzymes were 3 times greater than normal, in 9 patients (4.7%) enzymes showed 4 to 5 times increase, and 7 patients (3.6%) had increase greater than 5 times normal; 6 cases of the last group were over 30 years old. From 49 patients only 13 cases had jaundice with increased liver enzymes (Table II).

16 patients (8.4%) had increased bilirubin following treatment and 13 cases (6.8%) had this increase associated with increase in AST and ALT. From 16 patients who had increased bilirubin level, 5 cases had bilirubin level between 3-7.5 mg/dL and the rest had a bilirubin level between 1.2 to 3 mg/dL. Disturbance in PT was observed in 7.6% and alkaline phosphatase was in-

Table II: Liver enzymes (AST-ALT) after treatment in 190 patients.

Liver Enzymes	Number	Percent
Normal	141	74.2
Increase to 3 times the normal level	33	17.3
Increase 4 to 5 times the normal level	9	4.7
Increase greater than 5 times normal	7	3.6

creased in 18.4%.

During the treatment, 7 patients died (3.6%), 4 cases had tuberculous meningitis, 2 had active pulmonary TB and 1 suffered from miliary TB.

DISCUSSION

A six month regimen with isoniazid, rifampicin, pyrazinamide and ethambutol for the initial two months followed by rifampicin and isoniazid for a further four months is recommended as standard treatment for tuberculosis.[1,2,16,19] INH, RMP and PZA are associated with significant potential of causing hepatotoxicity. Asymptomatic elevation of liver enzymes occurs in 10-20% of patients who are treated with isoniazid.[1,2,18,19] In our study asymptomatic elevation in liver enzymes was 17.3%. The reported incidence of hepatotoxicity reactions in different studies are much higher (8-50%) in India and other developing countries[20,22,23] compared to those from developed countries (2-3%) despite using similar regimens.[19,20,22,23]

In the USA hepatotoxicity is reported in 3% with rifampin/isoniazid.[20]

Lesobre and associates described 12 cases of jaundice with 4 deaths among 50 patients receiving INH and RMP (24%) although many of these had pre-existing liver disease[7] and Lees et al. observed 4 cases with jaundice among 50 patients (8%) without known antecedent liver disease.[7] In our study 16 cases from 190 patients had jaundice (8%) without antecedent liver disease, similar to Lees et al's study.

Lal and others reported elevated AST, ALT in 28%.[7] In our study elevated AST, ALT was seen in 25.7% but we had hepatitis with jaundice and elevation in AST, ALT only in 8%. In another study from Iran by Ramezani and associates increase in liver enzymes was 2.3%.[12] The reason for relatively higher incidences of hepatotoxicity in India and developing countries (8-50%) is not clear. It has been suggested to be due to various factors such as older age, higher alcohol intake, malnutrition, intestinal parasitism, past history of jaundice, chronic liver disease, and viral hepatitis which is particularly prevalent in India.[10,17,22,23] It would be advantageous to identify this high risk group as toxic hepatitis complicates the management of tuberculosis; once identified, these patients can be monitored carefully for hepatotoxicity as antituberculosis treatment-induced hepatitis causes a mortality of 6-12% if the drugs are continued after the onset of symptoms.[6,17,18]

CONCLUSION

Considering that 25.7% of the patients had increased levels of liver enzymes and in 3.6% of them the level exceeded 5 times greater than normal and also 6 out of seven of these were over 35 years old, therefore anti-tuberculosis drug therapy, especially in patients over the age of 35, must be taken seriously.

A baseline liver function test at the beginning of treatment and repeated weekly for two weeks then two-weekly for the first two months is required for patients with known chronic liver disease and in older patients. During medical consultations in the course of anti-TB treatment, all patients should be assessed clinicaly for symptoms and signs suggestive of hepatitis and medication should be stopped if significant clinical symptoms occur or AST, ALT levels rise to 3-5 times the normal value or the bilirubin level rises.[2,3,19]

Finally, there should be a systematic effort to carry out surveillance for severe reactions to anti-tuberculosis therapy.

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