Indian J Physiol Pharmacol 1995; 39(1) : 43-46

ANTI TUBERCULAR TREATMENT INDUCED HEPATOTOXICITY : DOES ACETYLATOR STATUS MATTER?

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(Received on November 1, 1993)

Abstract: Anti tubercular drug related hepatotoxicity is common. The mechanism of injury and factors predisposing to its development are not fully understood. Forty patients with anti tubercular drugs related hepatotoxicity were studied to see the clinical and biochemical profile of these patients and to find out the significance of acetylator phenotype in the development of hepatotoxicity. Mean age of patients with liver damage (37.82± 10.0 years) was similar to those without liver damage (36.48±12.5 years). Pyrazinamide appeared to increase the hepatotoxicity of isoniazid and rifampicin. The percentage of rapid acetylators and slow acetylators among patients with hepatotoxicity (70% and 30% respectively) was similar to controls (66.6% rapid and 33.3% slow acetylators). Acetylator phenotype probably has no role in anti tubercular drugs induced hepatotoxicity.

Key words: antitubercular therapy hepatotoxicity acetylator status pyrazinamide isoniazid rifampicin

INTRODUCTION

Hepatotoxicity is a potentially serious side effect of otherwise generally safe and effective antitubercular treatment regimens comprising of isoniazid, rifampicin and pyrazinamide (1, 2). Isoniazid (INH) causes asymptomatic elevation of transaminases in about 10-20% of patients (3) and it leads to hepatitis in about 1% of patients (4). INH induced hepatitis can be fatal in 8-10% patients after the appearance of jaundice (5, 6).

The mechanism of INH induced hepatitis remains unclear. Direct toxic effect and hypersensitivity both have been incriminated as pathogenic mechanisms (7, 8). It has been observed that rifampicin, a hepatotoxic drug *per se* (9) adds to the hepatotoxicity of INH (10). Acetylator status of the individual has been considered as a possible factor in the development of hepatotoxicity. In different studies both fast acetylators (8, 11) as well as slow acetylators (12, 13) have been found to be at a higher risk of developing drug induced hepatitis when isoniazid and rifampicin have been used together. On the other hand, acetylator status has been found to be of no significance in another study (14). Thus, the issue whether fast or slow acetylators of INH are susceptible to increased hepatotoxicity remains unsettled. The present study was planned to find out the clinical and biochemical profile of patients developing anti tubercular treatment (ATT) induced hepatotoxicity and to see if acetylator status is an important determinant of INH induced liver injury.

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METHODS

Patients : This study included 40 patients with ATT induced hepatotoxicity attending the out patients department or admitted to the wards of All India Institute of Medical Sciences, New Delhi. Patients receiving ATT but developing acute viral hepatitis and those patients in whom hepatic disease was attributed to a cause other than ATT were excluded from the study. A similar group of 45 patients on ATT but without hepatotoxicity were also studied to serve as controls. Informed consent was obtained from all patients before inclusion in the study.

All study patients and controls underwent a thorough clinical and investigative work up. A proforma was completed noting the details of the name, age, sex, site and severity of tuberculosis, method of diagnosing tuberculosis, past history of liver disease, alcohol intake, ingestion of other potentially hepatotoxic drugs, blood transfusion in the past and other risk factors for the development of hepatic diseases such as health professionals, needle prick injury, intravenous drug addiction, sexual promiscuity etc. The details of the ATT being taken was recorded which included nature of drugs, dosage and duration of treatment.

Investigations included hemogram, Mantoux test, chest X-ray, abdominal ultrasonography, serum biochemistry (sugar, urea and electrolytes) and liver function tests (LFT). LFT included serum bilirubin, serum alkaline phosphatase, serum transaminases (SGOT and SGPT), prothrombin time, serum total protein and albumin. Hepatitis B virus surface antigen (HBsAg) was done in all patients to rule out hepatitis B virus infection.

Acetylator status was estimated using "Sulphadimidine test" (SDM test). In patients who were on ATT, all drugs were stopped at least 48 hours prior to SDM test. In patients with liver dysfunction due to ATT the acetylator status was determined after the liver functions returned to normal. SDM test was done as described previously by Rao et al (15). In short SDM was administered in the doses of 44 mg/kg orally in a fasting state. Blood was collected 6 hours later and serum separated and stored at –20 C for further analysis for SDM metabolites.

Follow up : Patients were followed up every week after the detection of hepatic injury and clinical and biochemical parameters were noted. ATT was withdrawn, changed, altered or restarted depending on these parameters.

Statistical analysis was carried out by applying student's 't' test for continuous variables and chi-square test with 'yates' correction for dichotomous variables. P values of less than 0.05 were regarded as significant.

RESULTS

The study group comprised of 40 patients who developed ATT induced hepatotoxicity. Their clinical characteristics are given in Table I. There was no difference between the control group and study group with regard to age and sex distribution (mean age 36.48±12·5 years in controls and 37·82±10·0 years in study patients; 27 males, 18 females in control group and 23 males and 17 females in study group).

TABLE I : Clinical characteristics of patients.

	Cases (n=40)	*Controls (n=45)*
Age (mean ±SD) years	37.82±10.01	36.48±12.58
Sex (M:F)	23:17	27:18
Chronic liver disease	3	4
Chronic alcoholism	2	4
HBV carriers	0	2
Acetylator status	21:9	28:14
Rapid : Slow	(70%:30%)	(66.6%:33.3%)

Time of appearance of hepatotoxicity : The interval between the start of ATT and development of hepatic injury varied from 3 days to 20 weeks with a mean of 32.4±33.5 days. In the majority of patients (70%) hepatitis was evident within the first month of starting ATT. The duration of drug intake in patients without liver damage varied from 6-9 months. LFT

profile of study patients and controls is provided in Table II.

TABLE II : Liver function test in patients with hepatotoxicity and controls.

	ATT induced hepatitis patients	*Controls*
Serum bilirubin (mean+SD) (mg/dl)	5.97 ±4.72	0.78±0.20
Serum alk. phosphatase (mean±SD) (KAU)	14.50 ±3.74	9.84±2.45
SGOT (mean±SD) (μ/l)	402.35±631.97	27.42±4.99
SGPT (mean ± SD) (μ/l)	428.36±620.96	27.95±7.95

Three out of 40 patients in study group and 4 out of 45 patients in the control group had evidence of chronic liver disease. Two patients in the control group and none in study group were HBsAg carriers.

Acetylator status : Acetylator status was estimated in 30 out of 40 patients who developed ATT induced hepatitis while in the control group 42 out of 45 patients underwent acetylator status estimation. Twenty one patients (70%) were rapid acetylators and 9 (30%) were slow acetylators in the study group. In the control group 28 patients (66.6%) were rapid acetylators while 14 (33.3%) were slow acetylators

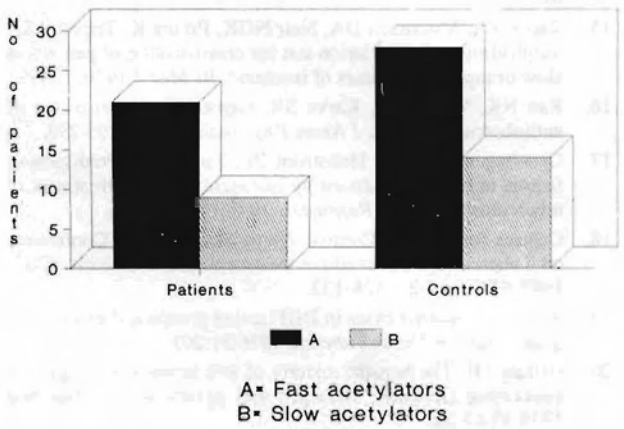

Fig. 1 : Bar diagram showing comparative numbers of fast and slow acetylators in study and control groups.

(Fig.1). There was no statistically significant difference between the two groups as regards the acetylator status.

INH (300 mgm/day) and rifampicin (450 mgm/day) were used in the initial chemotherapeutic schedule of all the patients in the study and control groups. Pyrazimaide (1-1.5 gm/day) was used in 70% of patients who developed hepatotoxicity while it was used in 38% of patients who did not develop hepatotoxicity. This difference was statistically significant (P<0.01).

ATT induced hepatitis proved fatal in 6 out of 40 patients i.e. a mortality of 15%. Four of these 6 patients died after developing fulminant hepatic failure while two patients died of subacute hepatic failure secondary to ATT. In the remaining 34 patients, the duration of ATT induced hepatitis varied from less than a week (4 patients) to more than a month (2 patients) but was 1-2 weeks in the majority.

DISCUSSION

ATT induced hepatitis is reported to occur in 2-39% of patients (10,13,16). Why only some patients develop liver injury due to anti tubercular drugs is not clearly understood. Various factors which are incriminated as possible factors predisposing to ATT induced liver injury are age > 50 years, female sex, alcoholism, chronic liver disease, hepatitis B virus carrier state, acetylator phenotype etc. (11,13,17-19). In the present study, 40 patients who developed hepatotoxicity were in the age group of 14-54 years. Males outnumbered females among those with liver injury. Presence of hepatitis B virus carrier state and chronic liver disease were not found to predispose to the development of hepatic injury. There is controversy in the literature over the potential of pyrazinamide in causing liver injury with evidence present both for (20) and against (21). In the present study, pyrazinamide appeared to be associated with increased risk of development of hepatotoxicity in a significant number of patients when added to INH and rifampicin. However, this points needs validation in a large number of patients.

There have been reports to suggest that rapid acetylators are more prone to develop liver injury (11)

because of increased amount of acetyl isoniazid formation in these patients. Acetyl isoniazid is converted to monoactyl hydrazine which is metabolised to other compounds causing liver damage (8). Other reports showed that slow acetylators were susceptible to INH toxicity (13) because of increased production of hydrazine after hydrolysis of INH to isonicotinic acid and hydrazine by isoniazid hydrolase (12). Hydrazine is supposed to be the hepatotoxic substance. However, in the present study we did not find any significant difference between groups of patients with or without ATT induced liver damage as regards the acetylator phenotype. Although the number of rapid acetylators was more than the slow acetylators among patients who developed ATT induced liver damage, the proportion of rapid and slow acetylators between the study and control groups was similar. This finding is in accordance with the observation made by Gurumurthy et al in South Indian patients (14). The mortality rate of 15% in our group of patients is considerably high. This probably can be explained by the fact that our hospital is a tertiary care referral hospital and more sick patients are referred to this institute which may result in increased mortality rate and may not be truly representative of mortality due to ATT induced hepatitis in a field setting.

We conclude from our study that ATT induced hepatotoxicity is commonly observed and may prove to be fatal. In addition to INH and rifampicin, pyrazinamide also possibly adds to hepatotoxicity. The acetylator phenotype of an individual either rapid or slow, is not a predisposing factor for the development of ATT induced hepatitis.

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