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EVALUATION OF RISK FACTORS FOR ANTITUBERCULOSIS DRUGS-INDUCED HEPATOTOXICITY IN NEPALESE POPULATION

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ABSTRACT

Antitubercular drugs cause derangement of hepatic functions revealed by clinical examination and abnormal liver function test. Many factors are found to predispose patients towards this adverse reaction of anti-tubercular drugs, which can cause economical burden as well as prolong duration of illness. Detection of these risk factors for hepatotoxicity can play an important role in minimizing the incidence. The present study had obejectives to assess the role of age, sex, alcohol intake, nutritional status and disease extent as risk factors in the development of hepatotoxicity in patients with active tuberculosis receiving antituberculosis treatment. 50 patients diagnosed of active tuberculosis infection with normal pretreatment liver function were monitored clinically as well as biochemically in a prospective cohort analysis. Four patients (8%) developed drug-induced hepatotoxicity. Antitubercular drugs-induced hepatotoxicity was prevalent in younger patients (6% vs. 2%, $P > 0.05$, $P = 0.368$, Odds Ratio [OR]; 2.75). Female gender was found to be at higher risk ($P > 0.05$, $P = 0.219$, Odds ratio [OR]; 4.2). Majority of the patients who had developed hepatotoxicity were sputum smear positive ones with advanced tuberculosis infection. Nutritional status, assessed by body mass index (BMI) and serum albumin level, was the next predisposing factor. Risk factors of hepatotoxicity included female sex, disease extent and poor nutritional status. Timely detection and temporary withdrawal of the offending agent can completely cure antitubercular drugs-induced hepatotoxicity.

Key words: tuberculosis, isoniazid, rifampicin, pyrazinamide, hepatotoxicity, and liver function test.

INTRODUCTION

Directly observed treatment short course (DOTs), based on WHO framework was introduced in Nepal in 1995 for effective control of TB.[1] Isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) have been successful therapeutic agents for the treatment of TB because of high therapeutic efficacy and good patient acceptance. However a variety of adverse reactions have been reported; one of the well-known toxic effects is hepatotoxicity.(Parthasarathy RG 1986; Koponoff DE 1978; Garibaldi RE 1972; Snider DE 1992) The risk is enhanced when these drugs are used in combination. Most cases of anti-TB drugs-induced hepatotoxicity are mild (i.e. asymptomatic with <3-fold elevation of serum ALT and AST) and commonly resolve despite taking continued therapy. However, some patients taking anti-TB drugs develop severe hepatitis that may progress to liver failure and death if drug is not stopped promptly (Timbrell JA, 1985).

Identification of patients at increased risk for anti-TB drugs–induced hepatotoxicity is important because hepatotoxicity causes significant morbidity and mortality and may require

modification of drug regimen. However, factors predicting anti-TB drugs-induced hepatotoxicity is still controversial. The primary objective of this study is to assess the risk factors for anti-TB drugs-induced hepatitis; that is to elucidate the relationship between age, gender, alcoholism, nutritional status, and disease extent with DIH.

METHODS

Patients

The study was conducted in the TB clinic, German Nepal Tuberculosis Project (GENETUP), from December 2001 to November 2002. The study comprises 37(74%) patients with active pulmonary TB and 13(26%) with active extra pulmonary TB infection. Among 13, 6 had tuberculous pleural effusion and 7 with tuberculous lymphadenopathy. There were 28(56%) male and 22(44%) female, with ages ranging 15 to 57 years (mean 30.5±14.5 years) (Table 1).

The patients fulfilled following criteria: they were negative for HBsAg, anti-HCVAb, and HIV. At the beginning of treatment, liver function tests showed completely normal findings on serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase (ALP), albumin and total protein. Patients receiving other potential hepatotoxic drugs in addition to anti-TB drugs and the relapsed cases of TB were excluded. 50 patients who fulfilled above stated criteria were selected during the study period. Patients gave written informed consent after approval by the ethical committee.

Drug regimens

Treatment was planned as recommended by our National Tuberculosis control Programme (NTP). Total treatment period was 8 months. Patients were given Directly Observed Treatment, Short course (DOTS) by medical staffs of the clinic Daily doses were as follows: INH: 300mg/day for all body weight, RMP: 300 mg (for 25-39 kg), 450 mg (40-54 kg), 600 mg (≥ 55 kg), PZA: 1000 mg (25- 39 kg), 1500mg (40-54 kg), 2000 mg (≥ 55 kg), E: 800 mg (25-39 kg), 1000 mg (40-54 kg), 1200 mg (≥ 55 kg).

Diagnosis of Drug-induced hepatotoxicity[7]

Following criteria were used to define anti-TB drugs-induced hepatotoxicity:
Normalization of liver enzymes level and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti-TB drugs, and presence of at least one of the following criteria:

- A rise to five or greater than five times the normal level of ALT and/or AST.
- A rise in the level of serum total bilirubin over 1.5 mg/dl.
- Any increase in AST and/or ALT above pretreatment levels together with anorexia, nausea, vomiting and jaundice.

Normal maximum value in the laboratory is 35 IU/L for ALT and 40 IU/L for AST. For ALP normal upper limit is 115 IU/L.

STUDY DESIGN

Liver function was monitored by measuring the serum level of AST, ALT, ALP, bilirubin (total and direct), total protein, and albumin with the help of an auto-analyzer in the pathology lab of Dhulikhel Hospital.

Pretreatment LFTs were conducted. After initiating the drug therapy, LFTs were performed after a week, then biweekly for at least two months. LFTs were repeated later whenever

symptoms suggestive of hepatotoxicity like nausea, anorexia, malaise, vomiting, organomegaly or jaundice occurred. Patients were kept under close observation and were instructed to report any unusual signs and symptoms they will come across during their treatment period.

In the patients developing hepatotoxicity, medications were stopped immediately and serum transferases were measured twice weekly, until symptoms resolve and the transferases level decreases down to 2 × ULN.[8]

Data analysis

Incidence of hepatotoxicity was determined from the rate of hepatic adverse reaction cases obtained from population beginning anti-TB therapy.

Elevations in serum AST and ALT levels (pretreatment vs. peak serum enzyme level during the treatment period) were analyzed by paired t-test. Statistical analysis was performed using SPSS version 10.0. Rates of hepatotoxicity due to anti-TB drugs were calculated for several subgroups of the cohort (male vs. female, elder patients aged > 35 vs. younger patients aged 15 - 35, alcoholic vs. non-alcoholic). Comparisons of rated were done by means of the Fisher's exact test using Epi Info, version 6.00

RESULTS AND DISCUSSION

During the 6-month study period, 4 patients out of 50 patients taking anti-TB drugs, developed hepatotoxicity detected by clinical examination and confirmed by liver function tests. The time interval from initiation of treatment to the onset of hepatotoxicity was 12 - 60 days (median of 28days).

It was analyzed that administration of antitubercular drugs caused elevations of liver enzymes in all the cases though it was only to the slight extent in most of the patients.
Patients who showed elevation in transferases (> 3 × ULN but < 5 × ULN) were continuing their anti-TB regimen, but under strict observation. Fortunately, their enzyme levels normalized within a few days of continued treatment.

Symptoms shown by all four patients developing hepatotoxicity were almost same. They had shown gastrointestinal manifestations like nausea, vomiting, abdominal discomfort, anorexia and jaundice. Due to this anti-TB therapy were stopped temporarily until their clinical and biochemical picture normalized.

Patients belonging to younger age group were found to be at higher risk for anti-TB drugs-induced hepatotoxicity (6% vs. 2%, P> 0.05, P=0.368, Odds Ratio [OR]; 2.75). Transferases index of patients belonging to younger and the older age groups were almost the same. Female gender was found to be another predisposing factor (P>0.05, P=0.219, Odds ratio [OR; 4.2]. Body mass index of our patients were low (BMI < 20kg/m^2) and their serum albumin levels were less than 3.5 mg/dl. Malnourishment may be one of the risk factors of anti-TB drugs-induced hepatotoxicity. Three patients developing hepatotoxicity had positive sputum smear. They had advanced TB infection, proven microbiologically as well as radiologically. Probably, the extent of disease has a role in predisposing the patient towards hepatotoxicity.

Anti-TB drug-induced hepatotoxicity is one of the most prevalent drug-induced liver injuries. Identification of patients at increased risk for DIH is important because hepatotoxicity causes significant morbidity and mortality and modification of drug regimen may be required.

In the present study, four out of fifty patients, which accounts for 8%, developed hepatotoxicity. The incidence obtained is much higher than previous studies from USA and UK (Timbrell JA, 1985). The incidence of hepatotoxicity has been reported to be higher in developing countries, and factors such as acute or chronic liver disease, poor nutrition, widespread parasitism, chronic infections, indiscriminate use of various drugs, ethnic factors, severity of the disease, chronic alcoholism or genetic predisposing may play a role individually or collectively(Kumar A 1991; Ungo JR 1998).

Incidence of anti-TB drugs-induced hepatotoxicity was found to be higher in younger patients, a finding that is in variance with experience of others (Mitchell JR 1978; Dorteh S 1995) (Table 2). We found female gender as another independent predictor of anti-TB drugs-induced hepatotoxicity (Snider DE 1992; de Souza AF 1996; Singh J 1996; Leff DR). Difference in the incidence of DIH between male and female is mainly due to; 1.Pharmacokinetic variations; probably, slower biotransformation and subsequent clearance of exogenous molecules due to lower level of microsomal enzymes. 2. It is also believed that women are slow acetylators. Slow acetylator enzymatic pattern shows male: female ratio of 4:1. Due to being a slow acetylator, females are more predisposed to the risk of hepatotoxicity (Gronhagen Riska C 1995; Marwin W 1998).

Nutritional status (assessed by body mass-index and serum albumin) (Mehta S 1990) of our patient seems poor (mean BMI = 18.7 kg/m2, serum albumin level = 2.8 mg/dl). It may be one of the risk factor for the DIH (Yi-Shin Huang 2002; Turktas M 1994; Dossing M 1996). We found that patients with pretreatment hypoalbuminaemia had a two fold higher risk of developing hepatotoxicity. In malnutrition, glutathion stores are depleted which makes one vulnerable to oxidative injury. In a malnourished person liver metabolizes drug at a slower pace. In a study done in India, incidence of hepatotoxicity was found to be three times higher in malnourished patients (Pandle JN, 1996).

We found no correlation between hepatotoxicity and alcoholism. Patients who had history of chronic alcohol intake continued treatment without any complications.[19]Extensiveness of the disease was also found to be the risk factor for anti-TB drugs-induced hepatotoxicity (Singh J 1995). Three patients developing hepatotoxicity were sputum smear positive and had moderately advanced TB infection. Incidences of hepatocellular damage may be due to tubercle bacilli products liberated in the liver after their destruction by anti-TB drugs (Singh J 1996).

Patients enrolled in the study were taking combination of anti-TB drugs. Due to this reason, it is difficult to conclude which drug was the main culprit for causing hepatitis (Leff DR). Although, INH is the major drug incriminated to induce hepatic injury, role of other possible hepatotoxic drugs (RMP and PZA) can also be speculated. Previous studies conducted have proven that the risk is in the order of INH + RMP>INH>PZA>RMP>E (Krishnaswamy K 1997).

INH produces hepatotoxicity by metabolic idiosyncratic reaction. Mild elevation of liver enzymes within few days of initiating antituberculosis drugs in the entire patient is probably due to INH. PZA is also considered a major hepatotoxin as INH. PZA used in addition to

INH and RMP in TB patients significantly raises the risk of anti-TB drug–induced hepatitis (Dorteh S 1995; Turktas M 1994; Tsagropolou Stinga H 1985; Altman C 1993). The exact mechanism of hepatotoxicity caused by PZA is not known. RMP is considered to be less hepatotoxic but is a powerful enzyme inducer, which may enhance INH hepatotoxicity (Garibaldi R 1972; Timbrell JA 1985; Singh J 1995). Formation of hydrazine, which is the key intermediate of INH metabolism and which is a potent acylating agent capable of causing liver necrosis is facilitated by RMP. Steele et al. also reported in their, meta-analysis that INH and RMP given together produce hepatotoxicity more than INH without RMP (Steele MA 1991). Since INH, RMP and PZA are always given in combination, it is difficult to diagnose the drug causing hepatotoxicity.

Hepatotoxicity can cause permanent injury and death. Early recognition of DIH with immediate withdrawal of offending agent is very important to arrest its development and allow liver to heal. British Thoracic Society suggests that if there is a rise in ALT and/or AST to greater than 3 times normal, or a rise in bilirubin, or if the patient showed clinical symptoms of hepatitis then drugs should be stopped and reintroduced sequentially when these parameters falls to previous levels. In the present study, abnormalities of liver biochemistries and symptoms shown by these four patients suggested discontinuing the treatment. Within few days of cessation of drugs, liver enzymes returned to the normal level. This normalization of the liver enzymes levels once the administration of the regimen has been halted proves that all signs and symptoms shown by the patient are related to the administration of anti-TB drugs (de Souza AF 1996; Singh J 1996; Altman C 1993).

Current American Thoracic Society center for disease control recommends adequate monitoring (clinical as well as biochemical) of individuals in order to avoid unnecessary morbidity and mortality, hence decreasing the cost of illness. TB patients usually belong to poor socioeconomic status and they cannot afford regular LFTs. Close monitoring of the patient's physical condition can be done in such situations. Clinical rather biochemical monitoring is used by many TB clinics, not only in Nepal but also in foreign countries according to the study done by Leff and Leff (Leff DR).

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Table 1: Baseline demographic characteristics of TB patients

Characteristics, Age, yr	**Total patients, n = 50 30.5 ± 14.5 yrs**
Sex, M/F	28/22
Height, m	1.520 ± 0.1
Weight, kg	42.8 ± 6.427
BMI, Kg/m^2	18.7 ± 2.5
Albumin level	2.8 ± 1.6

Data are presented as mean± SD except sex (M/F)
M = Male, F = Female, BMI = Body mass index

Table 2: Age, gender, disease extent, alcohol intake, albumin level, BMI – specific rate of hepatotoxicity in person receiving antituberculosis drugs (December 2001 to November 2002)

Parameters and number of patients	**Cases of hepatotoxicity**	**Rate of hepatotoxicity (%)**
Total patients, n = 50	4	8
Sex,		
Male n = 28	1	3.5
Female n = 22	3	13.6
Age,		
15-35 n = 27	3	11.1
36-60 n = 23	1	4.3
Disease extent		
Sputum positive n = 37	3	8.1
Sputum positive n = 13	1	7.7
Alcohol intake,		
Yes n = 9	0	0
No n = 41	4	9.8
Albumin level, g/dl		
≥ 3.5 n = 22	1	4.5
< 3.5 n = 28	3	10.7
Body Mass Index, kg/m^2		
≥ 20, n = 15	1	6.7
< 20, n = 35	3	8.6