Original Article

Risk Factors of Hepatotoxicity During Anti-tuberculosis Treatment

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Abstract

Background: Antituberculosis treatment (ATT) induced hepato-toxicity is common, but risk factors predicting its development are poorly understood. The present study evaluates the clinical risk factors predicting the development of hepatotoxicity in Indian patients with tuberculosis on antituberculosis treatment.

Methods: Three groups of patients were studied at three service hospitals over a 3 year period from 2000-2002. Patients given ATT were followed up with monthly LFTs. Consecutive patients who developed Liver dysfunction (rise in SGPT > 5 times upper limit of normal) were studied, along with matched controls who did not. Markers for hepatitis B were also noted in these patients once in 6 months. A third group of patients who did not receive ATT but were HBsAg positive, were also similarly followed up. The possible association of age and sex of the patient, alcoholism, unrecognized chronic liver disease, hepatitis B virus carrier status and nutritional status with ATT-induced hepatitis was assessed. Statistical analysis was carried out by Chi square test/Fisher's exact test using WHO provided software Epi Info 6. Sixty-nine patients with ATT-induced hepatotoxicity were prospectively studied. In addition 128 patients on anti-tuberculosis drugs without hepatotoxicity and 39 HBsAg carriers not on ATT were followed up for 1 year.

Results: Age, Sex, history of alcohol intake and BMI were not found to be related to development of hepatotoxicity. Presence of HBV infection or an underlying silent chronic liver disease were found to significantly increase the risk of development of ATT-induced hepatotoxicity. Continuation of ATT after development of jaundice was associated with a high fatality rate. It was possible to re-introduce isoniazid in 96% and rifampicin in 88% of patients with ATT induced hepatotoxicity.

Conclusion: ATT-induced hepatitis is common and is potentially fatal. It is likely to occur in those with underlying silent chronic liver disease, HBV infection and have been given ATT without a definite evidence of tuberculosis. Discontinuation of ATT leads to rapid recovery in most cases and drugs can safely be introduced after recovery in a majority of cases.

MJAFI 2006; 62 : 45-49

Key Words: Antituberculosis treatment; hepatotoxicity; malnutrition

Introduction

Tuberculosis is a common problem in India and worldwide, especially after the recent increase in incidence of acquired immunodeficiency syndrome (AIDS)[1]. Drug-induced hepatotoxicity is a potentially serious adverse effect of antituberculosis treatment (ATT) regimens containing isoniazid, rifampicin and pyrazinamide [2]. A higher risk of hepatotoxicity has been reported in Indian patients than in their Western counterparts[3,4]. The risk of hepatotoxicity based on data from four prospective Indian studies was 11.5% compared with 4.3% in Western publications [5]. The underlying mechanism of ATT-induced hepatotoxicity and the factors predisposing to its development are not clearly understood. The age and sex of the patients, chronic alcoholism and chronic liver disease, hepatitis B virus carrier status, acetylator status and nutritional status have all been incriminated as possible predisposing factors in earlier studies. However, contradictory results have been reported by other workers and consensus regarding their role is lacking [6,7]. Role of genetic factors has been suggested by some workers [8]. There are no definite recommendations as to whether ATT should be continued or stopped and what should be the schedule for reintroduction of these agents [9]. In view of above, the present study was undertaken to study the role of predictive markers for development of ATT-induced hepatitis and to test a pre-defined strategy of reintroduction of ATT for the treatment of tuberculosis in patients with ATT-induced hepatotoxicity.

Material and Methods

The study was conducted in two parts. First part was aimed at studying relationship of ATT-induced hepatotoxicity with HBsAg carrier state,[10] while second part was aimed at studying clinical spectrum of ATT induced hepatotoxicity. For the first part, all patients given ATT from medical OPDs at

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Received :05.02.2004; Accepted :19.01.2005

two service hospitals over a 2 year period from 2000-2001 were followed up with monthly LFTs. In addition, all patients who were HBsAg positive, had normal LFTs at inclusion and were referred from various centers for evaluation of HBV infection were also followed up. Liver function tests were monitored monthly and viral markers once in 6 months. Liver biopsy was planned whenever the ALT was twice the upper limit of normal on 3 consecutive tests. Liver dysfunction was described as rise in ALT> 5 times the upper limit of normal. For the second part, 69 patients with ATT-induced hepatitis seen at Gastroenterology centers of three service hospitals formed the study group. The criteria followed for diagnosing hepatitis were clinical manifestations of hepatitis along with serum aminotransferase levels more than 5 times the normal upper limit. Patients with tuberculosis who received the full course of ATT without developing hepatitis formed the control group. These patients were started on ATT at service hospital and were followed up regularly while they were receiving ATT. In all patients who presented to us with acute hepatitis while on ATT, sera were analysed for the presence of markers of acute viral hepatitis A, B, C and E (IgM anti-HAV, IgM anti-HEV, HBsAg, IgM anti-HBc and anti-HCV antibodies by ELISA respectively). We excluded those patients whose results of serologic tests indicated that the acute hepatitis was of viral origin. The details of ATT received including the nature of drugs, dosage and duration, patient compliance and intake of other potentially hepatotoxic agents including alcohol were recorded. A daily consumption of more than 40 g of alcohol for at least five years was considered as chronic alcoholism. The nutritional status of patients was estimated by calculating the body mass index (BMI) (weight in kg/height in mt^2). Malnutrition was considered to be present if BMI was less than 18.5 [11]. The presence of chronic liver disease was established by liver function tests, endoscopy, ultrasonography and liver biopsy (wherever possible). A complete liver function profile including serum bilirubin, serum aminotransferase, total protein and serum albumin, serum alkaline phosphatase and hepatitis B virus surface antigen was carried out in all patients of both groups.

After the detection of ATT-induced hepatitis, the likely offending drugs (INH, RMP and PZA) were discontinued. These patients were followed up every week until the clinical and biochemical parameters of hepatic injury became normal. During this period, antituberculosis drugs devoid of hepatotoxic potential (streptomycin and ethambutol) were given to the patient. We used a fixed schedule for the reintroduction of INH, RMP and PZA (if indicated) after the clinical and biochemical resolution of hepatitis [3]. On day 1, INH was introduced at a dose of 50 mg/day. If no rise in serum bilirubin and aminotransferase was observed on day 4, the dose was increased to 100 mg/day. Similarly, the dose of INH was increased to 200 mg/day on day 7 and to 300 mg/day on day 14. RMP was introduced after observing the patient for another 7 days. If the duration of PZA therapy before the onset of hepatitis had been <2 months, it was also reintroduced after RMP had been tolerated well for 7 days without evidence of hepatotoxicity. Follow-up was carried out once in 2 weeks on two occasions and then once every month until the completion of ATT.

The qualitative variables were analyzed by chi-square test with Yates correction. For the comparison of quantitative data, the Student's t test was applied. Values of $p < 0.05$ were regarded as significant. The results are expressed as the mean ± SD.

Results

First part of the study [10] consisted of 152 patients on antituberculosis drugs. Of these, 24 had chronic HBV infection. Additional 39 patients with HBV infection not on ATT were also followed up prospectively. The incidence of liver dysfunction was significantly higher in patients with chronic HBV infection on ATT (9/24, 37.5%) in comparison to both the control groups, i.e. (a) patients given ATT who had no evidence of HBV infection (13/128, 10.2%, p=0.0018) and (b) patients with chronic HBV infection who were not on ATT (5/39, 12.8%, $p < 0.05$). Patient with chronic HBV infection on ATT, who developed liver dysfunction were older ($p < 0.01$) and had more severe liver injury ($p < 0.05$) as compared to those who were HBsAg negative.

Second part of study evaluated 69 patients with ATT induced liver dysfunction. The age of these patients ranged from 17 to 79 years, the mean age being 39.7 ± 18.3 years. The male-to-female ratio of these patients was 47 males to 22 females. (Table-1)

Pulmonary tuberculosis followed by abdominal tuberculosis was the most common definite indications for starting ATT in our patients. (Table-2) However, single largest group among the study patients was one where ATT was given empirically without clear diagnostic evidence.

The clinical presentation of ATT-associated hepatitis was not different from that of acute viral hepatitis. Twenty-two patients (31.8%) experienced symptoms suggestive of prodrome associated with acute viral hepatitis (anorexia, nausea, vomiting and upper-abdominal discomfort) but without jaundice. Jaundice, in association with some of the above-mentioned symptoms, was the presenting feature in 47 (68.1%) patients. Manifestations of hypersensitivity reaction (skin rash, drug fever, eosinophilia etc.) was uncommon and seen in 5 patients. The values of various liver function tests during follow-up are shown in Table 3.

Table 1

Characteristics of the 3 groups of patients studied

	Patients (ATT induced otoxicity)	HBV carriers not on ATT	Controls on ATT
Numbers	69	39	128
Age (years)	39.7 ± 18.3	31.5 ± 21.1	43.8 ± 27.7
Sex M:F	47:22	32:7	44:26
Chronic alcoholism	6	1	5 (8.33%)
Chronic liver disease	7	6	3 (2.34%)
HBV carriers	13	39	0
BMI	18.02 ± 3.40	22.18 ± 3.75	18.50 ± 3.33

Table 2

Primary diagnosis of cases for which ATT was started

Primary diagnosis	No. of patients (%) with hepatotoxicity (n=69)	No. of patients without hepatotoxicity	p value
Pulmonary	20 (28.9)	62 (51.7)	0.008
Abdominal	15 (21.7)	18 (14.1%)	0.17
Disseminated	5 (7.2)	15 (11.7)	0.32
Lymph node	4 (5.8)	16 (12.5)	0.137
Spinal	3 (4.3)	6 (4.7)	0.91
Pericardial	1 (1.4)	3 (2.3)	0.67
Empirical*	21 (30.4)	8 6.3)	M 0.0001

Note : *Presumptive diagnosis of tuberculosis without any definite evidence included cases of exudative ascites (9), PUO (5), weight loss (4) and abdominal lymph nodes.(3)

Table 3

The values of various liver function tests recorded during the serial follow-up of patients with ATT induced hepatotoxicity. Mean (±SD) as well as the range is shown.

	Mean ± SD	Range
Serum bilirubin (mg/dl)	6.54 ± 5.98	1.4 - 22.0
Serum albumin (G/dl)	3.4 ± 1.8	2.4 - 5.1
AST (U/L)	768.4 ± 526.0	210 - 3440
ALT (U/L)	570.3 ± 505.1	160 - 3080
ALP (U/L)	210.4 ± 122.4	150 - 370
INR	2.1 ± 1.9	0.9 - 7.2

There was no significant effect of age or sex on the incidence of hepatotoxicity. Similarly, history of alcohol intake did not increase the incidence of ATT induced hepatotoxicity (p=0.162). Presence of HBsAg in serum or an underlying silent chronic liver disease were significant risk factors in development of ATT-induced hepatotoxicity (p= <0.001 and 0.017 respectively). Malnutrition did not play a significant role as a risk factor as long as drug dosages were correct as per body weight.

Fifty-two of 69 patients with ATT-induced hepatitis had an uncomplicated course. The clinical and biochemical resolution of hepatotoxicity was observed within 3 weeks of stopping ATT and duration of hepatotoxicity ranged from 1 week (2 patients) to > 1 month (3 patients). Seventeen patients developed serious complications from ATT-induced hepatitis (Table 4). Fourteen patients developed hepatic encephalopathy. Of these 5 were subsequently found to have underlying chronic liver disease while remaining 9 were classified as fulminant hepatic failure. Three patients developed subacute hepatic failure with gross ascites. One patient with chronic liver disease, 2 with subacute hepatic failure and 4 with fulminant hepatic failure succumbed.

The mean age of patients with fatal complications (47.1 years) was significantly higher as compared to others with ATT-induced hepatitis (38.9 years). Similarly, in patients who died, the duration of treatment before recognition of hepatitis (42.5 ± 28.6 days) was significantly longer compared with that in others (33.2 ± 29.4 days)(p < 0.05). The duration of jaundice before the onset of encephalopathy in patients with

Table 4

Clinical profile of ATT induced hepatitis (n=69)

Complication	No. of patients	Percentage	Deaths	Percentage of complications
Acute uncomplicated hepatitis	52	75.4	0	0
Fulminant hepatic failure	9	13	4	30.8
Hepatic encephalopathy	5	7.2	1	20
Subacute hepatic failure	3	4.3	2	66.7
Total	69	100	7	—

fulminant hepatic failure (FHF) ranged from 3 to 11 days, with a mean of 5.9 ± 3.4 days. Highest levels of S. bilirubin were also higher among fatal cases in comparison with non fatal cases (Mean of 10.4 versus 6.1 mg/dl). None of the patients who died was a hepatitis B virus carrier. In 5 of the 7 patients who died, hepatotoxic ATT was, for some reason, not stopped even after jaundice was clinically apparent to patient. Significantly, 3 of the 7 fatal complications occurred in patients who had received ATT empirically.

Reintroduction of potentially hepatotoxic drugs was attempted in 41 patients with evidence of active tuberculosis and in 8 cases where ATT was started empirically. We reintroduced one drug at a time as per protocol under close supervision. It was possible to introduce Isoniazid in 47 (96%) and rifampicin in 43(88%). In remaining patients, recurrence of hepatotoxicity prevented further reintroduction. Pyrazinamide reintroduction was attempted only in 12 patients and had to be discontinued in 4 due to development of altered LFTs.

Discussion

The incidence of hepatotoxicity among patients on ATT was 10.1%, which is similar to that reported in Indian studies [5,12]. Our data with 69 patients with ATT-induced hepatotoxicity shows that this adverse drug reaction is common and is potentially fatal. In our experience, nearly one fourth develop serious complications, such as fulminant and subacute hepatic failure, with 7 patients (10%) ending fatally. Referral bias may partly explain a relatively high morbidity and mortality seen in this series, which has been collected primarily at tertiary care hospitals. In literature, there is a wide disparity in the reported incidence of ATT-induced hepatitis ranging from 2 to 39% [2,5]. The incidence has been reported to be higher in developing countries and factors such as acute or chronic liver disease, indiscriminate use of drugs, malnutrition and more advanced tuberculosis have been implicated [13,14]. The reported mortality from ATT-induced hepatitis after the development of jaundice varies from 4-12% [15].

Why only some patients who receive ATT develop

hepatitis is not clear and several studies searched for host factors, environmental factors or some interaction among various factors. While some papers have focused on genetic factors, such as HLA typing [8], Cytochrome P450 2E1[20] or acetylator status,[13] others have primarily studied clinical factors, as the present study.

Some studies have reported that the risk of ATT-induced hepatitis increases with advancing age, the highest incidence being in individuals older than 50 years [14]. In the present study, no significant correlation of age with ATT-induced hepatotoxicity was found. However, once hepatotoxicity developed, fatal out come was much more likely among the older patients (mean age 47.1 years as compared to 38.9 years in non fatal cases). We did not find any sex preponderance in our study. Such a lack of sex difference has been reported earlier [6]. Some workers have reported that women are more prone to develop ATT-induced hepatitis [15]. Contrary to observations in earlier studies [17] no significant difference was found in the prevalence of alcohol intake among patients in the study and control groups.

Significantly, highest incidence of hepatotoxicity was noted in the group of patients where ATT was given empirically without a definite diagnosis of tuberculosis. Nearly half the fatalities occurred in this group. Two of the three patients who died had high protein ascites due to cirrhosis, which was mistakenly diagnosed as abdominal tuberculosis. This observation must force us to reconsider the decision to institute a therapeutic trial of ATT in undiagnosed cases, which many consider a standard mode of diagnosing abdominal tuberculosis. If ATT is deemed necessary as a therapeutic trial in some situations or if it is used as preventive therapy, regular monitoring of liver function tests should be mandatory.

Presence of HBsAg in serum or an underlying silent chronic liver disease were found to be a major and significant risk factor in development of ATT-induced hepatotoxicity. One report from Taiwan suggested that there is a higher incidence of ATT-induced fulminant and subacute hepatic failure in hepatitis B virus carriers compared to noncarriers [18], though some other studies have failed to notice any difference[19]. Another study has reported that the presence of chronic liver disease does not confer any additional risk of ATT-induced hepatitis.

Low nutritional status is considered to be one of the factors contributing to relatively high incidence of ATT-related hepatitis in studies from developing countries [20]. Drug metabolism pathways including acetylation pathway have been shown to be deranged in states of protein energy malnutrition [21]. In the present study, the BMI of patients with ATT-induced hepatitis was not significantly different from that of patients in the control group and very few patients with poor nutrition were seen. A high incidence of viral hepatitis has been reported to coexist in patients with tuberculosis in developing countries, [22] resulting in misdiagnosis of ATT-induced hepatotoxicity, especially if serologic tests are not performed. All patients with positive serologic tests for hepatitis A, B, C and E were excluded from the current study.

In the patients who died, the period that elapsed between the initiation of ATT and the appearance of hepatotoxicity was significantly longer than in the other patients with ATT-induced hepatitis. Similar observations have been made earlier in patients with INH-associated hepatitis[23,24]. Continued subtle damage leading to serious hepato-cellular injury could be a possible etiology [3]. The short duration of jaundice (mean 5.9 days) before the development of encephalopathy in 9 patients with FHF marks the rapidity with which severe liver failure can develop in some patients following ATT. There are reports in literature of patients who developed idiosyncratic reactions to ATT and required liver transplantation [25].

The treatment of underlying tuberculosis after the detection of ATT-induced hepatitis is often difficult. A few studies have offered a systematic approach to reintroducing ATT in such a situation [3] though some earlier studies have shown that reintroduction of ATT can be risky [26]. Several regimens have been tried to re-introduce ATT, some starting with isoniazid and others with rifampicin or pyrazinamide. In general, pyrazinamide containing regimens have been found more hepatotoxic [27,28,29,30]. We were able to safely reintroduce isoniazid and rifampicin in most of our patients (96% and 88% respectively) after recovery from hepatitis. Although such attempts to reintroduce potentially hepatotoxic ATT-drugs might generate some concern regarding safety, it is inevitable as it is the only effective and rapidly acting regimen, requires much shorter duration of treatment and prevents risk of development of resistance. We reintroduced ATT in a stepwise manner both with regard to the specific drug and the dosage and this strategy proved to be fairly effective and safe. Careful monitoring of patients treated with the latter approach with periodic liver function tests is essential.

In conclusion, ATT-induced hepatotoxicity runs a mild course in the majority of patients but may lead to serious complications, such as acute liver failure, with resultant mortality in others. The antituberculosis drugs with a potential to cause hepatitis can usually be safely reintroduced after recovery from ATT-induced hepatitis.

Summary

ATT-induced hepatitis is common. Various clinical factors that might predispose to the development of ATT-induced hepatitis have been studied. The present study has shown that the development of ATT-induced hepatotoxicity was not influenced by age, sex, alcohol intake or malnutrition. This complication was likely to occur in those who had underlying chronic liver disease, hepatitis B carrier status and in those where the prescription of ATT was given without a definite evidence of tuberculosis. Fatality due to ATT induced hepatotoxicity was more likely when jaundice occurred over 6 weeks after the starting of ATT, serum bilirubin was higher and where ATT was continued despite appearance of jaundice. Discontinuation of ATT leads to rapid recovery in most cases. The antituberculosis drugs with a potential to cause hepatitis can usually be safely reintroduced after recovery from ATT-induced hepatitis.

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