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Study of Anti-Tuberculosis Treatment Associated Hepatotoxicity and Related Risk Factors

KEYWORDS: Antitubercular treatment; hepatotoxicity; malnutrition; Alcohol; Hepatitis B.

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ABSTRACT *Our study evaluates the clinical risk factors associated with the development of hepatotoxicity in patients with tuberculosis on antitubercular treatment. Three groups of patients were studied over 1 year period in 2014-2015. Patients given ATT were followed up with monthly LFTs. Consecutive patients who developed liver dysfunction (rise in SGPT > 3 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 state and nutritional status with ATT-induced hepatitis was assessed. In addition 128 patients on anti-tuberculosis drugs without hepatotoxicity and 39 HBsAg carriers not on ATT were followed up for 1 year. We found that 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 was 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. Discontinuation of ATT leads to rapid recovery in most cases and drugs can safely be introduced after recovery in a majority of cases.*

Introduction

Drug-induced hepatotoxicity is a potentially serious adverse effect of antituberculosis treatment (ATT) regimens containing isoniazid, rifampicin and pyrazinamide. A higher risk of hepatotoxicity has been reported in Indian patients than in their Western counterparts. The risk of hepatotoxicity based on data from four prospective Indian studies was 11.5% compared with 4.3% in Western publications. 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. 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

We studied relationship of ATT-induced hepatotoxicity with HBsAg carrier state and clinical spectrum of ATT induced hepatotoxicity. 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 mt2). Malnutrition was considered to be present if BMI was less than 18.5. 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 aminotransferases, total protein and serum albumin, serum alkaline phosphatase and hepatitis B virus surface antigen was carried out in all patients. 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 aminotransferases 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

Out of 152 patients on antituberculosis drugs 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%) 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

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HBsAg negative. Out of 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. Pulmonary tuberculosis followed by abdominal tuberculosis was the most common definite indications for starting ATT in our patients. 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 abovementioned symptoms, was the presenting feature in 47 (68.1%) patients. Manifestations of hypersensitivity reaction (skin rash, drug fever, eosinophilia etc.) were uncommon and seen in 5 patients. 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 fulminant hepatic failure (FHF) ranged from 3 to 11 days, with a mean of 5.9 ± 3.4 days. 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.

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	

Discussion

The incidence of hepatotoxicity among patients on ATT was 10.1%, which is similar to that reported in Indian studies. 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%. 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. The reported mortality from ATT-induced hepatitis after the development of jaundice varies from 4-12%. 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. Drug metabolism pathways including acetylation pathway have been shown to be deranged in states of protein energy malnutrition. 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, 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. Continued subtle damage leading to serious hepato-cellular injury could be a possible etiology. 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.

Conclusion

Our 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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