MEDICAL CHANNEL

Original Article

FREQUENCY OF HEPATOTOXICITY DURING ANTI-TUBERCULOUS TREATMENT AT MEDICAL UNIT OF LUMHS SINDH

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ABSTRACT

Objective: To evaluates the frequency of development of hepatotoxicity in patients with tuberculosis on antituberculous treatment presenting in department of Medicine Liaquat University of Medical and Health Sciences Jamshoro.

Methodology: This prospective, descriptive study was carried out on five hundred diagnosed patients with tuberculosis, during March 2008 to March 2011. In this study tuberculous patients were included who were consecutively admitted in department of medicine or attended medical out-patient department of Liaquat University of Medical and Health Sciences (LUMHS) Jamshoro. The patients, who developed hepatitis, while they were on antituberculous therapy, were evaluated. The criteria for diagnosing hepatitis were clinical manifestations of acute hepatitis along with rise in serum liver enzymes by three times from baseline and excluding other causes of rise in enzymes. In all patients who presented to us with acute hepatitis while on antituberculous therapy, sera were analysed for, liver function tests and the presence of markers of acute viral hepatitis A, B, C and E. The patients who developed viral hepatitis were excluded from study. Patients with tuberculosis who received the full course of antituberculous therapy without developing hepatitis formed the control group; they were compared with patients who developed hepatitis due to antituberculous therapy.

Statistics: The results are expressed as the mean ± SD. For the comparison of quantitative data, the Student's t test was applied using SPSS 16. Values of $p < 0.05$ were regarded as significant.

Results: The age of these patients ranged from 15 to 80 years, the mean age being 41.8 ± 17.6 years. The male-to-female ratio of these patients was 300(60%) males to 200(40%) females. Pulmonary tuberculosis was the most common definite indications for starting ATT Table-1. 55 patients (11%) out of 500 developed ATT-induced hepatitis. Five (1%) patients with antituberculous treatment induced hepatitis died Table 2. The mean age of patients with fatal complications in our study was 50.1±3.5 years. The values of various liver function tests during follow-up are shown in Table 3.

Conclusion: It was concluded that ATT-induced hepatitis is not an uncommon problem in field of Medicine.

Key Words: Antituberculous treatment; hepatotoxicity.

INTRODUCTION

Tuberculosis is a common problem in subcontinent and worldwide, especially after the recent increase in incidence of acquired immunodeficiency syndrome. According to the World Health Organization there were an estimated 9.27 million new cases of tuberculosis worldwide in 2007[1]. Pakistan ranks eighth on the list of 22 high-burden tuberculosis countries with an estimated 743 new cases of tuberculosis annually. Multi drug-resistant tuberculosis (MDR-TB) and XDR-TB (eXtensively drug-resistant tuberculosis) are the greatest health hazards for those infected with HIV/AIDS[2]. Abdominal tuberculosis commonly affects the intestinal tract. Isolated hepatobiliary or pancreatic tuberculosis

is rare and the preoperative diagnosis is difficult[3]. Almost all anti-tuberculous drugs as (Isoniazid, Rifampicin, Pyrazinamide, Ethionamide), with the exception of Ethambutol, Aminoglycosides and Cycloserine can cause hepatitis. The frequency of hepatitis is low with large studies analyzed from all over the world suggesting an incidence of 0 - 5%. Although a moderate rise in serum transaminases is commonly observed in early weeks of therapy (Isoniazid 12 to 18%, Rifampicin-14%, Pyrazinamide 10%, Ethionamide 10%), it resolves spontaneously in majority of cases. In case a 5-fold rise is seen in enzymes from basal values, anti-tuberculous treatment should be discontinued until enzymes return to normal[4]. The risk of hepatotoxicity with Isoniazid increases with age and also in alcoholics. It has been postulated that rifampicin may increase hepatotoxicity due to Isoniazid in slow acetylators by inducing the enzyme hydrolase. With Pyrazinamide, the risk of hepatotoxicity increases with preexisting liver disease, as well as with dose and duration.

Rifampicin and Isoniazid are not contraindicated in patients with past history of liver disease, in hepatitis-B carriers and in alcoholics. Pyrazinamide is contraindicated in patients with preexisting liver disease because the half life of Pyrazinamide (10 hours in patients with normal hepatic and renal functions) is prolonged in patients with impaired hepatic functions. Drug-induced hepatotoxicity is a potentially serious adverse effect of antituberculous treatment regimens containing isoniazid, rifampicin and pyrazinamide[5]. The underlying mechanism of antituberculous treatment-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 large number of patients on anti tuberculous treatment in province of Sind Pakistan, the present study was undertaken to study the frequency of liver dysfunction due to anti tuberculous treatment.

METHODOLOGY

This prospective, descriptive study was carried out on five hundred diagnosed patients with tuberculosis, during March 2008 to March 2011. In this study tuberculous patients were included who were consecutively admitted in department of medicine or attended medical out-patient department of Liaquat University of Medical and Health Sciences (LUMHS) Jamshoro. All patients were given antituberculous treatment for various reasons as pulmonary tuberculosis, abdominal tuberculosis, tuberculous meningitis and other types of tuberculosis. After subjective improvement patients were asked for outdoor weekly follow up for the period of anti tuberculous therapy. The patients, who developed hepatitis, while they were on antituberculous therapy, were evaluated. The criteria for diagnosing hepatitis were clinical manifestations of acute hepatitis along with rise in serum liver enzymes by three times from baseline and excluding other causes of rise in enzymes. Patients with tuberculosis who received the full course of antituberculous therapy without developing hepatitis formed the control group; they were compared with patients who developed hepatitis due to antituberculous therapy.

In all patients who presented to us with acute hepatitis while on antituberculous therapy, sera were analysed for, liver function tests, as serum bilirubin, Serum albumin, Alanine aminotransferase ALT, Aspartate aminotrasferase AST, Alkaline phosphatase ALP, International normalized ratio INR. 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). We excluded those patients whose results of serologic tests indicated that the acute hepatitis was of viral origin. The details of antituberculous therapy received including the nature of drugs, dosage and duration, patient compliance; and intake of other potentially hepatotoxic agents including drugs & alcohol were recorded. The presence of chronic liver disease was established by liver function tests and ultrasonography.

STATISTICS

The results are expressed as the mean ± SD. For the comparison of quantitative data, the Student's t test was applied using SPSS 16. Values of $p < 0.05$ were regarded as significant.

TABLE 1
PRIMARY DIAGNOSIS OF CASES OF TUBERCULOSIS FOR WHICH ATT WAS STARTED N500

Primary Diagnosis	Total No of Patients n 500	No of Patients with hepatotoxicity n55	No of Patients without hepatotoxicity n 445
Percentage	(100%)	(11%)	(89%)
Pulmonary	292(58.4%)	36	259
Abdominal	90(18%)	09	81
Disseminated	30(06%)	04	26
Lymph Nodes	15(03%)	01	14
Spinal	05(01%)	00	05
Pericardial	03(0.8%)	00	03
Empirical	65(13%)	05	60

TABLE 2
CLINICAL PROFILE OF ATT INDUCED HEPATITIS N=55 (11%) AND MORTALITY (1%)

Complications	No of Patients (55)	Percentage (100%)	Mortality
Acute uncomplicated hepatitis	40	(72.7%)	(0)
Fulminant hepatic failure	05	(09.1%)	(4)
Hepatic encephalopathy	10	(18.2%)	(1)

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
N 55

PARAMETERS	LFT prior to ATD		LFT after liver injury		
	Mean ±SD	Range	Mean ±SD	Range	P value
Serum bilirubin (mg/dl)	0.408 ±0.196	0.22-0.9	9.09 ± 8.18	2.46-35	0.0009
AST (U/L)	36.9±7.9	23-38.8	585±526	130-2100	0.0017
ALT (U/L	25.1 ±4.87	15-30.8	546±660	141-2850	0.0049
ALP (U/L)	68.1±26.3	35.5-150	188.±32.1	170-260	0.0001
INR	1.07 ±0.205	0.8-1.38	2.34 ±1.39	0.7-5.8	0.0001

ATD— ANTITUBERCULOUS THERAPY

RESULTS

In this study five hundred tuberculous patients were included. The age of these patients ranged from 15 to 80 years, the mean age being 41.8 ± 17.6 years. The male-to-female ratio of these patients was 300(60%) males to 200(40%) females. Pulmonary tuberculosis was the most common definite indications for starting ATT Table 1. The largest group among the study patients was one where ATT was given empirically. The clinical presentation of ATT-induced hepatitis was same as that of acute viral hepatitis. 55 patients (11%) out of 500 patients developed ATT-induced hepatitis and experienced symptoms suggestive of prodrome associated with acute viral hepatitis (anorexia, nausea, vomiting and upper-abdominal discomfort) with jaundice. Forty (8%) out of 55 patients with ATT-induced hepatitis had an uncomplicated course. The clinical and biochemical resolution of hepatotoxicity was observed within 6 weeks of stopping ATT. Fifteen (3%) patients developed serious complications from ATT-induced hepatitis. Ten (2%) patients developed hepatic encephalopathy. 5 (1%) patients were subsequently found to have underlying chronic liver disease while remaining 5 (1%) patients were classified as fulminant hepatic failure. Five (1%) patients with antituberculous treatment induced hepatitis died Table 2. The mean age of patients with fatal complications in our study was 50.1±3.5 years. The values of various liver function tests during follow-up are shown in Table 3. Liver function tests are significantly deranged in patients with ATT induced hepatitis as evident from p value less than 0.05.

DISCUSSION

It has been recognized that despite approximately one third of the world's population being infected with Mycobacterium tuberculosis, less than 10% of infected individuals are potentially threatened to develop pulmonary tuberculosis during their lifetime[10]. The frequency of hepatotoxicity among patients on ATT is 11% in our study, which is similar to that reported in other studies [5%,10%,12%]. In one study the incidence of jaundice was 8.2% which is higher than previously reported studies and those who developed jaundice (72.7%) were above 35 years; therefore, it was recommended that patients who are more than 35 years of age and receiving ATT should be closely watched for evidence of drug induced hepatitis[11]. Our data with 55 patients with ATT-induced hepatotoxicity shows that this adverse drug reaction is common and is potentially fatal. In our experience, nearly one fourth developed serious complications, such as fulminant hepatic failure, with 5 patients (1%) ending fatally Table 2. In a study done on tuberculous patients jaundice was the presenting symptom in 44 (61%) patients; prodromal symptoms were present in 28 (39%). Serious complications developed in 12 (16.6%) patients[12]. Rifampicin, Pyrazinamide, and Isoniazid are known to cause liver injury; they cause hepatotoxicity and pancreatitis, which can lead to bile duct obstruction[13].

In literature, there is a wide disparity in the reported incidence of ATT-induced hepatitis ranging from 2 to 39%. In our study the frequency of hepatotoxicity among patients on ATT is 11%. 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[14]. The reported mortality from ATT-induced hepatitis after the development of jaundice varies from 4-12%[15]. In our study five (1%) patients with antituberculous induced hepatitis died which is less in comparison to other studies possibly due to early detection. Why only some patients who receive ATT develop hepatitis is not clear. Some studies have reported that the risk of ATT induced hepatitis increases with advancing age, the

highest incidence being in individuals who are older than 50 years[16]. In the present study the mean age of patients with fatal complications is 50.1± 3.5 years. 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[17], though some other studies have failed to notice any difference[18]. 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[19]. Drug metabolism pathways including acetylation pathway have been shown to be deranged in states of protein energy malnutrition[20]. A high incidence of viral hepatitis has been reported to coexist in patients with tuberculosis in developing countries[21], resulting in misdiagnosis of ATT-induced hepatotoxicity, especially if serologic tests are not performed. There are reports in literature of patients who developed idiosyncratic reactions to ATT and required liver transplantation[22]. In one study on 25 patients with tuberculous meningitis, two patients developed hepatitis improved on discontinuing pyrazinamide[23]. It has been observed that anti-tuberculosis therapy as well as tuberculosis preventive therapy can be safely employed in HIV and hepatitis co infected patients, if baseline liver function tests are within normal limits[24].

CONCLUSION

It has been concluded that ATT-induced hepatitis is not an uncommon problem in field of Medicine and discontinuation of ATT leads to rapid recovery in most cases.

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