HEPATOTOXICITY WITH ANTITUBERCULOSIS DRUGS: THE RISK FACTORS

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ABSTRACT

Objective: To assess the severity and frequency of hepatotoxicity caused by different antituberculosis (ATT) drugs and to evaluate whether concurrence of risk factors influence the antituberculosis drug induced hepatotoxicity.

Method: This prospective cohort study was conducted in Medical Unit-V and OPD department of Civil Hospital Karachi from July 2004 to July 2005. A total of 339 patients diagnosed of active tuberculosis infection with normal pretreatment liver function were monitored clinically as well as biochemically. Their data were collected on proforma and patients were treated with Isonized, Rifampicin and Pyrazinamide. Duration after which derangement in function, if any, occurred and time taken for normalization was noted. Treatment was altered as needed, with exclusion of culprit drug. Finally data was analyzed by SPSS version 10.0.

Results: ATT induced hepatotoxicity was seen in 67 (19.76%) out of 339 patients. Females were more affected as compared to males (26.3% vs. 19.7%). BMI (kg/m^2) of 91% of diseased group were less than 18.5 ($p<0.01$) most of them were anemic having low albumin level suggestive of lean body mass. Hepatotoxicity was more severe in AFB smear positive patients. Concomitant use of alcohol, paracetamol and low serum cholesterol were proved as predisposing factors. Isoniazid [37 patients (55.21%), $p<0.01$] was the main culprit followed by Rifampicin (23 patients, 34.21%) and Pyrazinamide (7 patients, 10.5%). Most of the patients (61%) developed the hepatotoxicity within two weeks of starting antituberculosis therapy with mild to moderate alteration in ALT and AST.

Conclusion: ATT-induced hepatitis is significantly more frequent and more severe in patients with hepatotoxicity risk factors.

KEY WORDS: Hepatotoxicity, Anti-TB drugs, Tuberculosis, Risk factors.

Pak J Med Sci January - March 2007 Vol. 23 No. 1 33-38

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* Received for Publication: March 2, 2006

* Accepted: September 30, 2006

INTRODUCTION

Tuberculosis has proved to be a menace for the human population in general and to the developing countries in particular as a widely prevalent infectious disease. WHO has declared that Tuberculosis is a global emergency.[1] An effective control has been achieved by the widespread use of anti tuberculosis drugs. However, despite their efficacy, superadded problems have to be faced in terms of long duration of treatment, emergence of MDR strains and certain adverse effects ascribed to these drugs. Among these adverse effects hepatotoxicity is a well known complication of Anti Tuberculous Therapy (ATT).[2-4] The severity ranges from alteration in liver enzymes, chronic active hepatitis and picture of acute hepatitis, occasion-

ally complicated by acute liver failure carrying very high mortality unless transplanted. It is common with Isoniazid especially when given in combination with Rifampicin and Pyrazinamide. Fifteen to 20 percent of patients receiving Isoniazid as a single agent for prophylaxis against tuberculosis may have increased serum alanine and aspartate aminotransferase levels, but only 1 percent have hepatic necrosis severe enough to require the withdrawal of the drug.[5] The clinical, biochemical and histopathological features of drug induced hepatotoxicity (DIH) are indistinguishable from that of viral hepatitis.[6] We do not have the exact data of drug induced hepatitis in Pakistan although Tuberculosis is a common problem in our country, but in UK and USA the incidence is 3 and 4 % respectively.[7]

Early identification and modification of treatment regimen are required for patients who are at increased risk of anti tuberculous induced hepatotoxicity and hence reducing the morbidity and mortality.

It has been postulated that hepatotoxicity induced by ATT is not truly idiosyncratic in essence. Rather certain genetic and environmental factors are attributed to coincide to produce sufficient quantity of toxic metabolites that then cause varied alterations in liver functions. ATT inducible cytochrome P-450 2E1 (cyp2E1) is constitutively expressed in the liver. Recent studies show that polymorphism of the N-acetyltransferase2 (NAT2) genes and glutathione-s transferases (GST) are the two major susceptibility risk factors for ATT induced hepatotoxicity.[8]

Reported risk factors for hepatotoxicity include: older age, female sex, poor nutritional status, high alcohol intake, pre-existing liver disease, hepatitis B carriage, increased prevalence of viral hepatitis in developing countries, hypoalbuminaemia and advanced tuberculosis, and inappropriate use of drugs and acetylator status.

We conducted this study on different varieties of tuberculous patients receiving ATT to know the severity and frequency of hepatotoxicity and the relationship between age, sex, nutritional status, alcoholism, disease extent, the cholesterol level and concomitant use of paracetamol with drug induced hepatitis.

PATIENTS AND METHODS

Patient Selection: This prospective cohort study was conducted in Medical Unit-V and Out Patient Department of Civil Hospital, Karachi, from 15 July 2004 to 14 July 2005 and they were selected according to inclusion and exclusion criteria.

Total 339 patients males were 183 (53.98%) and female 156 (46.02%) included who were prescribed to receive anti tuberculosis drugs for pulmonary or extra pulmonary tuberculosis. Among extra pulmonary involvement cases were diversified such as that of abdomen, spine/bones, meninges, lymphnodes, genital, skin, joints, pericardium or miliary spread. Only those tuberculous patients were considered eligible for recruitment that were being given Isoniazid, Rifampicin, ethambutol and Pyrazinamide according to their body weight as part of their treatment regime. Patients on ATT were excluded from the study if they had any of the following: having preexisting acute or chronic liver disease, baseline transaminases more than two times normal, patients' not receiving Rifampicin and Isoniazid as part of treatment, and fatty liver.

Study Design: All the patients had pretreatment evaluation clinically especially for evidence of liver disease, body weight and BMI, history of alcoholism or concomitant drug therapy and lab evaluation especially hemoglobin levels, serum albumin, serum cholesterol, LFTs and ultrasound abdomen. Malnutrition was defined as BMI<18.5 (kg/m^2). Viral markers were done to exclude viral hepatitis. Presence of fatty liver was excluded on the basis of ultrasonography. LFTs were repeated weekly for the first month then twice in next month and thereafter monthly till the completion of ATT. In patients having minor alteration in liver enzymes upto 3-5 times of normal, ATT was continued but with moderate alterations i.e. five to ten times of normal, they were keenly observed for signs of acute hepatitis or further rise in enzymes or appearance of jaundice. In such patients ATT was withheld and patients

were followed with repeated LFTs till normalization, after which ATT was reintroduced with Pyrazinamide followed by Rifampicin and then INH. In case patient again developed symptoms or signs of hepatotoxicity, the causative drug was then permanently excluded from the treatment. A person drinking more than six units (48 gm ethanol) per day for more than one year is considered as a risk factor.

Drug Regimen: Total treatment period of nine months comprising intensive phase of two months followed by continuation phase of seven months. Intensive phase comprises of daily Isoniazid (INH), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E). Streptomycin (S) was added to the initial treatment regimen replacing ethambutol whenever necessary. Continuation phase comprises of daily Isoniazid and Rifampicin. The dosages of drugs were: INH 5mg/kg/day (maximum 300mg/day), Rifampicin 10mg/kg/day, Pyrazinamide 20-25mg/kg/day, Ehambutol 15mg/kg/day and streptomycin 15mg/kg/day.

Diagnosis of Drug Induced Hepatotoxicity: Hepatotoxicity was defined as normalization of liver function after withdrawal of all anti-tuberculosis drugs, and the presence of at least one of the following criteria: (1) appearance of jaundice (2) a rise of five times the upper limit of normal levels (50 IU/L) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT); (3) a rise in the level of serum total bilirubin > 1.5mg/dl[9].

Data Analysis: Statistical analysis was performed by using SPSS version 10.0.

RESULTS

There were a total of 339 patients that were included in a prospective cohort analysis. Patients were predominantly males i.e. 183 (53.98%) versus 156 (46.02%) females. Ages of the patients ranged between 13 and 73 years with an average of 36 yrs. Body weight of the patients showed a wide variation with 19kg and 85kg at the 2 extremes and mean body weight was 31kg. Baseline biochemical evaluation showed levels of hemoglobin between 6.04 and 11.4gm%, SGPT between 22 & 56 I.U & serum cholesterol between 100 and 240mg%.

Table-I: Demographic Variables of Study Group

Variable	*Range*	*Average*
1. Sex	M=183, F=156	
2. Age (years)	13-73	36
3. Body weight (kg)	19 -85	31
4. Hb (gm%)	6.04-11.4	8.3
5. Baseline LFTs (SGPT) (I.U)	22 -56	
6. Serum cholesterol (mg%)	100-240	135
7. H/o alcoholism	8 patients	
8. Concomitant paracetamol intake	All patients	

Eight patients were known alcoholics and almost all patients admitted with concomitant use of paracetamol for various purposes. (Table-I). Patients of both pulmonary and extra pulmonary type of tuberculosis were included in the study. Out of these almost 56.9% (193 patients) had lung involvement whereas among the rest, abdominal 16.5% (56 patients), meningeal 8.0% (27 patients), lymph node 6.8% (23 patients) involvement were the major varieties (Table-II).

During the study period, 67 patients out of 339 (19.8%) taking anti-TB drugs, developed hepatotoxicity detected by clinical examination and confirmed by liver function tests. All these patients showed alteration in SGPT& SGOT but majority of them i.e. 38 (11.2%) patients had minor alteration of 3 to 5 times of normal. Fourteen patients were found to have severe derangements in SGPT & SGOT, while 15 patients showed moderate derangement. Bilirubin levels increased in 32 patients and again majority of patients i.e. 20 had mild increase of up to3gm percentage (Table-III).

Table-II: Different Varieties of Tuberculosis & Associated Hepatotoxicity

Type	*n*	*(%)*	*Hepatotoxicity (%)*	
Pulmonary	193	(56.9)	22	(11.3)
Abdominal	56	(16.5)	26	(46.4)
Spine/Bone	18	(5.3)	3	(16.6)
TBM	27	(8.0)	5	(18.5)
Miliary	9	(2.6)	4	(44.4)
Lymph node	23	(6.8)	4	(17.4)
Genital	3	(0.9)	1	(33.3)
Skin	2	(0.6)	0	
Joints/Arthritis	5	(1.5)	1	(20)
Pericardial effusion	3	(0.9)	1	(33.3)

Table-III: ATT Induced Alterations in LFTs

Hepatotoxicity occurred in 67 out of 339 patients: 19.76%			
	n	*Patients*	*n (%)*
SGPT	67	mild 3 to 5 times of normal (15-40)	38 (56.7%)
		moderate 5 to 10 times of normal (201-400)	15 (22.4%)
		severe >10 times of normal >400	14 (20.9%)
SGOT	67	2 to 5 times of normal	38 (56.7%)
		5 to 10 times of normal	15 (22.4%)
		>10times of normal	14 (20.9%)
BILIRUBIN	32	2 to 3 mg%	20 (62.5%)
		> 3 mg%	12 (37.5%)

Female sex was more affected as compared to males (41 out of 156) 26.3% vs. (36 out of 183) 19.7%. Patients of old age were relatively more affected than the younger age group (41 out 159, 25.8% vs. 26 out of 180, 14.4%) for ATT induced hepatotoxicity. The time interval from initiation of treatment to the onset of hepatotoxicity was recorded. Maximum number of patients (41 out of 67) developed hepatotoxicity with in 14 days of starting the therapy. Twenty patients had alteration in liver function within 2 to 4 weeks whereas rest of the patients showed alteration after one month of treatment. Almost four fifth of patients had normalization of their liver function tests within two weeks.

It was analyzed that hepatotoxicity was induced in maximum number of patients i.e. 37 out of 67 (55.21%) by Isoniazid, which is statistically significantly higher as compared to Pyrazinamide (P<0.01). Rifampicin was second to follow in 23 patients (34.31%) and Pyrazinamide was found to cause hepatotoxicity in 7 patients i.e. (10.4%).

Hemoglobin levels of almost 75% of patients fall in the range of moderate to severe anemia and almost their hemoglobin ranges between 6-10gm% which is significant statistically (P<0.05). In our study 91% of the diseased group showed BMI<18.5 ((kg/m^2) which is also significant statistically (P<0.01) and >90% had albumin level less than 3.5 Gm/dl suggestive of lean body mass that predisposes for hepatotoxicity. It was noticed that 17 out of 339 patients (5.01%) had hypocholesterolemia out of which 7 patients (41.2%) developed hepatotoxicity and 60 patients (18.63%) of normal cholesterol level also developed ATT induced hepatotoxicity. Paracetamol intake of more than 2gm daily lead to ATT induced hepatotoxicity in 33.8% of patients. Alcohol intake was proven as a risk factor in 25.5% of the diseased group (Table-IV). Patients suffering from abdominal tuberculosis were more affected with hepatotoxicity as compared to other types of tuberculosis and is statistically significant (P<0.05).

DISCUSSION

The wide prevalence of tuberculosis through out the world makes it social and economical burden especially for developing countries and the use of anti tuberculous drugs is an optimistic approach for this problem. However

Table-IV: Demography and risk factors of patients receiving ATT

Variables	*Cases of hepatotoxicity*	*Rate of hepatotoxicity %*
Total patients		
No.339	67	19.8%
Male n=183	36	19.7%
Female n=156	41	26.3%
Age		
13-40 years n=180	26	14.4%
41-73 years n=159	41	25.8%
Hemoglobin level		
6-8 gm %	17	25.4%
8.1-10 gm %	35	52.2%
>10 gm %	15	22.4%
BMI		
< 18.5 kg/m^2	61	91.0%
18.5-24.9 kg/m^2	6	9.0%
Albumin level g/dl		
> 3.5 n=111	5	4.5%
< 3.5 n=228	62	27.1%
Alcohol intake		
Yes n=8	2	25.0%
No n=331	62	19.6%
Paracetamol intake		
Up to 2gm/day n=221	27	12.2%
> 2gm/day n=118	40	33.8%
serum cholesterol level		
< 120mg/dl n=17	7	41.2%
140-240mg/dl n=322	60	18.6%
Disease extent		
Sputum positive	40	59.7%
Sputum negative	27	40.3%

certain reservations associated with its use need to be properly evaluated especially ATT induced liver injury and the predisposing factors that add to this hepatotoxicity.

This study was conducted to assess the role of age, sex, severity of the disease, nutritional status, alcoholism, use of paracetamol and effect of cholesterol as a risk factor for ATT induced hepatotoxicity. In our study 19.76% of the patients developed ATT induced hepatotoxicities that almost overlap the study conducted at Japan.[10] The combination of multi drug therapy for tuberculosis has been associated with increase risk of hepatotoxicity when compared with INH monotherapy used for TB prophylaxis.[11] The reported incidence of ATT induced hepatotoxicity is different in various countries though not fully understood but could be due to the characteristics and the risk factors of the population studied, the different diagnostic criteria used to define hepatotoxicity, different geographical areas, tests carried out during follow ups and the type of monitoring.[12]

A study conducted in Nepal[13] resulted in 8% and 13% in Hong Kong Chinese patients.[14] Four prospective Indian studies documented the risk of ATT induced hepatotoxicity as 11.5% compared with 4.3% in fourteen published studies from west.[15] Our study has clearly shown the higher incidence of ATT induced hepatotoxicity in female as compared to males (26.3% vs. 19.7%) and this result matches with previous studies conducted.[16-18] Vulnerability of females could be due to variations in pharmacokinetics and slow acetylation enzymatic pattern, resulting in hepatotoxicity.[19] Older age group was affected more as compared to younger one (25.8% vs. 14.4%) strengthening the previous studies.[20,21] Hemoglobin levels of three fourth patients fall in the category of moderate to severe anemia. Nutritional status of our patients was very poor and 61 patients (91%) BMI were below 18.5 (kg/m^2) and 27% of the patients showed the hypoalbuminemia and this may be one of the risk factors of ATT induced hepatotoxicity.[13-22] The possible explanation of ATT induced hepatotoxicity in malnutrition is depletion of glutathione stores that makes one vulnerable to oxidative injuries. Our study depicts the same result as a study conducted at India showing three times higher incidence of ATT induced hepatotoxicity in malnourished patients.[23]

Alcohol intake was proved to be a predictor for hepatotoxicity and 25% of patients showed this result. It was also seen in previous studies that patients who were taking ATT when used alone or in combination with alcohol may increase the risk for hepatotoxicity in patients taking acetaminophen.[24] Concomitant use of paracetamol predisposes for the liver injury as reported by A. Fernandez.[12] A few studies are denying the alcohol as a predisposing factor for ATT induced hepatotoxicity[12,25,26] possibly depending upon the dose and duration of alcohol as well. Forty patients (59.70%) were sputum smear positive and they were severely affected indicating the extensiveness of the disease also a risk factor[16,25-27] but we have also seen in 27 patients (40.3%) who were sputum smear negative and suffered from ATT induced hepatotoxicity. Severity of the disease in sputum smear positive patients could be secondary to, more tubercular bacilli in smear positive patients as compared to smear negative patients. ATT induced hepatotoxicity was seen in 41.2% of the patients with decreased cholesterol level[28] (below120mg/dl) and 18.6% with normal cholesterol level. However further studies are required for elaborating cholesterol as a risk factor.

In this study Isoniazid became a main culprit in 37 patients (55.2%) for ATT induced hepatotoxicity despite being the back bone of the tuberculous therapy. Isoniazid can cause asymptomatic, minor alteration in liver enzyme in initial days of treatment which do not require discontinuation of the drug.[23] INH produces hepatotoxicity by idiosyncratic reaction. Combination of Isoniazid with Rifampicin and Pyrazinamide increases the risk of ATT induced hepatotoxicity.[11,13,20,29] Rifampicin is relatively an innocent drug in comparison with Isoniazid but in our study it targeted 23 patients (34.31%) causing ATT induced hepatotoxicity. It is a powerful enzyme inducer which may enhance Isoniazid hepatotoxicity.[16] Pyrazinamide also claims seven patients

(10.5%) and is most hepatotoxic antituberculous medication like Isoniazid. The mechanism of hepatotoxicity has been considered to be dose related[23] but in one case report re challenge after an initial reaction to a combination regimen lead to an increase in serum aminotransferases level to eighty times the upper limits of normal with an associated eosinophila, suggestive of hypersensitivity reaction.[30]

CONCLUSION

ATT induced hepatotoxicity can cause permanent injury and death. Early recognition with immediate withdrawal of offending agent is very important to arrest its development and allow liver to heal. Thus correct association of predisposing factors that can augment the liver injury in the population being treated by ATT can significantly help in pointing out patients prone to develop it, the need to follow them up more closely, to identify hepatotoxicity at the earliest possible time to design new drug regimen and to decrease the load of mortality and morbidity caused by widely used anti tuberculous drugs. ATT induced hepatotoxicity is significantly more frequent and more severe in patients with a fore-mentioned risk factors.

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