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HEPATOTOXICITY OF ATT

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ABSTRACT... Objectives: To determine the frequency of hepatotoxicity with standard ATT. **Study design:** Descriptive. **Setting:** Department of Medicine, Combined Military Hospital Lahore. **Period:** Feb 2007 to April 2008. **Materials & methods:** 250 patients aged 18 years or greater having pulmonary TB were selected through non-probability convenience sampling technique. All patients were given four drugs for two months indoors, followed by two drugs for four months in outdoor. Symptoms suggestive of hepatotoxicity were enquired from the patients regularly. Serum bilirubin and ALT were measured on monthly basis and finally on completion of therapy. Hepatotoxicity was defined as a five fold rise in serum ALT. In patients developing hepatotoxicity, treatment was modified accordingly. **Results:** This study was done on 189 male and 61 female patients (total: 250). Hepatotoxicity developed in 13 (5.2%) patients, mostly during the initial phase of treatment (84.6% incidence during the first month). Risk factors included: age (4 out of 156 young patients and 9 out of 94 older patients; p: 0.016) and nutritional status (8 malnourished patients and 5 well nourished patients; p: 0.031). Hepatotoxicity was not related to the gender (9 males and 4 females; p: 0.585) or the results of baseline sputum smears (7 out of 102 smear positive cases and six out of 148 smear negative cases; p: 0.064). **Conclusions:** Hepatotoxicity with ATT is fairly common, especially in the elderly, malnourished patients and during the initial phase of treatment.

Key words: Hepatotoxicity, Tuberculosis, Rifampicin, Isoniazid

INTRODUCTION

Tuberculosis (TB) remains one of the most challenging public health problems of the 21st century, particularly in developing countries. According to World Health Organization, in Pakistan alone, the prevalence is 223 per 100,000 population[1]. Moreover, nearly 300000 new cases develop each year, most of which belong to the productive age group. The situation is worsened by the existence of poor socioeconomic conditions and illiteracy. Similarly, a poor healthcare system in the rural areas is responsible for the delays in diagnosis and improper treatment. In this modern era, a broad armamentarium of drugs is currently available for combating the disease. Considering the difficulties in mycobacterial eradication, the standard chemotherapy includes four drugs given simultaneously for two months, followed by two to three

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drugs for another six months. Treatment of multi-drug resistant TB and extensively drug-resistant TB is much more complex, falling into the domain of experienced pulmonologists.

The use of antituberculosis therapy (ATT) is associated with some adverse effects, particularly hepatotoxicity that most frequently occurs during first two months of therapy. These adverse effects often negatively affect the compliance which is crucial for curing TB; they may also require a change of treatment. Hepatotoxicity can be either dose dependent or idiosyncratic. The liver is especially vulnerable to damage because it is involved in metabolism and excretion of most drugs forming part of ATT. It is of great importance to identify patients developing hepatotoxicity quickly so as to alter the management plan in a way that TB continues to get cured and the morbidity and mortality associated with hepatotoxicity are also reduced.

This study was done to determine the actual magnitude of the problem in our setup. It is a step towards creating awareness about the problem amongst the general practitioners. These doctors must realize the gravity of the situation and understand that close monitoring is required for early detection of ATT- induced hepatotoxicity.

METHODS AND MATERIALS

This descriptive study was conducted on 250 patients at Department of Medicine, Combined Military Hospital Lahore from February 2007 to April 2008. All patients aged 18 years or greater having pulmonary TB, except those meeting the criteria listed below, were enrolled for the study after obtaining informed written consent.

EXCLUSION CRITERIA

Unwilling patients, those with deranged baseline serum bilirubin/ alanine transaminase (ALT), those known to have chronic hepatitis B or C virus infection or other significant co- morbid conditions, alcoholics and patients already on modified ATT were excluded.

TB was diagnosed on the basis of detailed history, thorough clinical examination & appropriate investigations including sputum smear for acid fast bacilli, chest X ray, erythrocyte sedimentation rate & mantoux test. Body mass index (BMI) measured in each patient at the time of admission was taken as a surrogate marker of nutritional status, with malnutrition being defined as BMI <18 kg/m^2. All patients were admitted to medical wards and started on a combination of following four drugs: isoniazid 5 mg/kg/ day, rifampicin 10 mg/ kg/ day, ethambutol 15- 25 mg/ kg/ day; and, pyrazinamide 25- 35 mg/ kg/ day. Patients were discharged from hospital after two months & followed up in out door. Pyrazinamide and ethambutol were stopped at this stage; rest of the drugs were continued for six months.

During the course of treatment, symptoms suggestive of hepatotoxicity (nausea, vomiting, loss of appetite, upper abdominal discomfort, and yellowish discolouration of eyes or deepening of urine colour) were enquired from the patients daily. Serum bilirubin and ALT were measured either periodically on monthly basis, or earlier whenever the patients developed any symptoms suggestive of hepatotoxicity, and finally on completion of therapy. Hepatotoxicity was defined as a five fold rise in serum ALT. Patients developing hepatotoxicity were to be readmitted (if already discharged from the hospital) and treatment modified to include amikacin (15mg/ kg BD), levofloxacin (500mg OD) and ethambutol (15- 25 mg/ kg OD) instead of standard ATT. Subsequent management included serum ALT monitoring and rechallenge with ATT as per American Thoracic Society guidelines[2].

Data was collected through a carefully designed structured questionnaire and analyzed using SPSS version 10. Personal information of patients was strictly kept confidential. Frequencies and percentages were computed to present all categorical variables as mean ± standard deviation. Results were compared amongst the two genders and also between patients younger than 45 or older, using student's t- test.

RESULTS

250 patients, including 189 (75.6%) males and 61 (24.4%) females, were enrolled for this study, none of

whom was excluded/ dropped at any point during the study period. Males were generally older (ages 38.83± 13.45 and 45.95± 17.27 years; p: 0.001) and heavier (weight 66.10± 6.07 kg and 54.69± 8.28 kg; p: 0.000) than females. Their gender- and age- wise biochemical profile is depicted in fig-1 and table-I respectively.

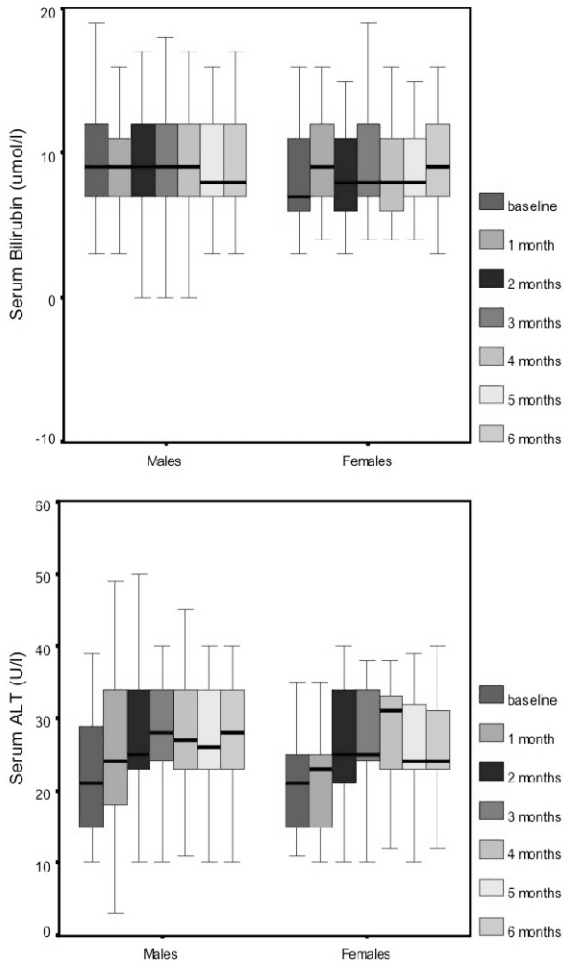

Fig 1. Biochemical profile of the study population

Acid fast bacilli (AFB) were seen on Zeihl Nelson staining of sputum in 40.8% cases. Mean ESR was 58± 16.83 mm fall at the end of first hour. Mantoux test was positive in 32% cases with a mean induration of 12.3± 3.65 mm.

Table-I. Biochemical profile compared between the two age groups.

	≥ 45 years	< 45 years	P-value
Serum bilirubin baseline (µmol/l)	8.75± 3.44	9.67±3.44	0.036
Serum bilirubin 1 month (µmol/l)	9.14± 3.18	9.27±3.01	0.745
Serum bilirubin 2 months (µmol/l)	9.50± 6.07	9.32±3.90	0.776
Serum bilirubin 3 months (µmol/l)	9.73± 3.98	9.30±3.57	0.375
Serum bilirubin 4 months (µmol/l)	9.12± 3.17	9.21±3.25	0.834
Serum bilirubin 5 months (µmol/l)	10.17±13.57	9.05±3.35	0.327
Serum bilirubin 6 months (µmol/l)	8.76±2.80	10.53±12.84	0.189
Serum ALT baseline (U/l)	21.39±7.17	22.05±8.01	0.514
Serum ALT 1 months(U/l)	41.71±55.90	30.49±34.41	0.051
Serum ALT 2 months (U/l)	37.15±36.70	27.79±14.23	0.005
Serum ALT 3 months (U/l)	30.59±13.82	28.38±8.89	0.126
Serum ALT 4 months (U/l)	27.81±8.08	26.89±7.41	0.360
Serum ALT 5 months (U/l)	25.93±7.32	26.81±7.68	0.368
Serum ALT 6 months (U/l)	26.53±8.04	27.13±7.76	0.562

Only 13 patients (5.2%) developed hepatotoxicity. Nine of them were males and rest females. Thus, 4.76% of males and 6.55% of females were affected. This gender difference, however, was not statistically significant (p: 0.585). There were 156 patients aged less than 45 years and 94 aged 45 years or greater.

Hepatotoxicity was diagnosed in 4 (2.56%) and 9 (9.57%) patients of both groups respectively, the difference being statistically significant (p: 0.016). Similarly, eight patients developing hepatotoxicity had BMI <18 kg/m^2 whereas five had BMI >18 kg/m^2 (p: 0.031). Seven of the patients developing hepatotoxicity were smear positive for AFB whereas the other six were not. This difference was however statistically insignificant (p: 0.064).

Frequency of new cases developing hepatotoxicity by the end of each month of therapy is depicted in table-II.

Table-II. Time frame for development of hepatotoxicity.

Month	Males	Females
1	8	3
2	1	1
3	0	0
4	0	0
5	0	0
6	0	0

It can clearly be seen that all cases occurred during the initial phase of treatment, more so commonly during the first month. Moreover, the frequency of various symptoms of hepatotoxicity in these patients is shown in table-III.

All the thirteen cases developing hepatotoxicity were readmitted to hospital and their treatment was modified as described in the section above. With an improvement in the clinical and biochemical picture, the modified treatment was gradually replaced with standard ATT. None of the patients developed hepatotoxicity again and all completed the course of ATT successfully. No patient died either as a result of the disease or due to the treatment.

DISCUSSION

The overall rate of hepatotoxicity is comparable to other studies carried out in this region[3]. This study recruited lesser number of female patients as compared to males.

Table-III. Frequency of side effects.

Side Effect	Males	Females	Total
Nausea	7(3.70%)	3(4.92%)	10(4.00%)
Vomiting	3(1.59%)	3(4.92%)	6(2.40%)
Loss of appetite	1(0.53%)	2(3.28%)	3(1.20%)
Upper abdominal discomfort	1(0.53%)	1(1.64%)	2(0.80%)
Yellow discoloration of eyes	1(0.53%)	1(1.64%)	2(0.80%)

This was because most families of the soldiers live away in their home towns and secondly, women are usually allowed to receive treatment as outdoor cases as per our hospital's policy. Nevertheless, among available patients, there was no gender difference in the incidence of ATT induced hepatotoxicity as also shown by Anand, et al[4]. The results, however, are in contrast to the international literature[5] and the findings of a study conducted at Civil Hospital Karachi, where hepatotoxicity was commoner in females (26.3% vs. 19.7%)[6]. In the latter however, the results were not compared amongst the two genders using any test of significance.

Old age is a recognised risk factor for ATT induced hepatotoxicity[7]. In this study, older patients were fewer than younger ones. This is because as per hospital policy, retired patients can receive therapy at home if desired in contrast to a soldier serving in the Army who has to receive ATT as an indoor case. Moreover, most elderly patients were found to have significant co- morbid conditions which excluded them from the study. But it was found that older age group was affected more as compared to younger one (9.57% vs. 2.56%; p: 0.016).
An England based study demonstrated that frequency of side-effects leading to modification of treatment was 2.3% in the 0–19 yrs age group in contrast to 8.4% for those aged above 60 yrs[7]. Older patients may be more vulnerable because of decreased hepatic drug metabolism by cytochrome-P450 enzyme system, and age related changes in liver blood flow, liver size, drug binding or distribution.

Hepatotoxicity was noticed to be more frequent in first two months of therapy, as also observed by Dhingra, et al[8]. It may most probably be due to use of combination of pyrazinamide along with rifampicin and isoniazid. In a recent study, seven out of twelve patients (58%) treated for latent TB with ethambutol and pyrazinamide developed transaminase elevation of more than four times the upper limit of normal[9]. Because ethambutol alone is not hepatotoxic, pyrazinamide was likely to be the offending agent. So this may be cause of increased hepatotoxicity during first two months of ATT. Malnutrition has also been shown to be a risk factor for hepatotoxicity, as already demonstated by a number of international studies[10].

Our study is limited by the fact that unfortunately we did not take into account the use of other potentially hepatotoxic drugs especially paracetamol/ NSAIDs which were routinely used as antipyretic and analgesic agents in the study population. Serum cholesterol and serum albumin were not measured and their role as risk factors for hepatotoxicity could not be evaluated. We also appreciate that hepatotoxicity to individual drug is more important than blaming just combined drug therapy but we could not formulate any means of identifying any individual drug as the responsible agent. More studies are required in this regard.

CONCLUSION

Hepatotoxicity due to ATT is quite a significant and common problem, being more prevalent in the elderly. All efforts must be made to identify such cases as soon as possible through regular clinical assessments and biochemical monitoring. It is worth while to appreciate that more stress must be laid on case identification during the initial two months of therapy.

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PREVIOUS RELATED STUDIES

Channa MS, Janjua MZ, Soomro MB, Sangi S. Protective role of anti-oxidant; against hepatotoxicity by ciprofloxacin in wistar albino rats. Professional Med J Sep 2003; 10(3):196-200.