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ANTI-TUBERCULOSIS THERAPY;

Derangement in liver enzymes among patients undergoing Anti-tuberculosis therapy.

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ABSTRACT… Objectives: Tuberculosis (TB) is a major cause of illness and death worldwide, especially in Asia and Africa. An effective control has been achieved by the widespread use of ATT. 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. Objective of the study was to determine the frequency of derangement of liver enzymes in patients taking anti-tuberculous therapy within the first 8 weeks of therapy. **Study Design:** A descriptive case series study. **Place and Duration of Study:** The study was conducted at the in-patient and out-patient department of general medicine of Pakistan Institute of Medical Sciences (PIMS), Islamabad for blood sampling and biochemical assays. **Material and Methods:** The study was performed on a total of 114 patients of tuberculosis. ATT was started after baseline liver function tests. Liver function tests were repeated at 4 weeks and 8 weeks to observe the effects on liver enzymes derangement. **Results:** 12 patients had deranged LFTs while 102 patients had normal LFTs after 4 weeks of treatment while 10 patients had deranged LFTs and 104 patients had normal LFTs after 8 weeks of treatment. **Conclusions:** Anti-tuberculosis drugs induced hepatotoxicity occurs less frequently. All patients put on anti-tuberculous therapy must be followed up for at least the initial 4 weeks, and the patient and caregivers should be told how to recognize signs of anti-tuberculous induced hepato-toxicity.

Key words: Anti tuberculosis therapy, Liver Function Tests, Tuberculosis.

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INTRODUCTION

Tuberculosis (TB), a multisystemic disease and it is the most common cause of infectious disease related mortality worldwide. The World Health Organization (WHO) has estimated that 2 billion people have latent TB and that globally, in 2009, the disease killed 1.7 million people. New TB treatments are being developed and new TB vaccines are under investigation[1,2]. Infection with M tuberculosis results most commonly from infected aerosol exposure through the lungs or mucous membranes. In immunocompetent individuals, this usually produces a latent/dormant infection; only about 5% of these individuals later show evidence of clinical disease.

M tuberculosis is a slow-growing, obligate aerobe and a facultative, intracellular parasite. The organism grows in parallel groups called cords. It retains many stains after de-coloration with acid-alcohol, which is the basis of acid-fast stains. The basic laboratory tests for the detection of tuberculosis include complete blood count, chemistries (ALT and AST), Alakaline Phosphatase, total bilirubin, uric acid, creatinine, etc.

Derangement of liver enzymes may be caused by INH, RIF, or PZA. An asymptomatic increase in AST concentration occurs in nearly 20 percent of patients treated with the standard four-drug regimen; in most patients asymptomatic aminotransferase elevations resolve spontaneously. Occasionally there are also

disproportionate increases in bilirubin and alkaline phosphatase; these are consistent with rifampin hepatotoxicity[3]. In general, antituberculosis agents should be discontinued if a patient's transaminase level exceeds three times the upper limit of normal in association with symptoms, or five times the upper limit of normal in the absence of symptoms. Drug-induced hepatitis is a diagnosis of exclusion; other possible etiologies must also be assessed such as acetaminophen, alcohol, and hepatitis A, B, or C. The optimal approach to resumption of antituberculous therapy is uncertain and expert consultation should be obtained. In general, in cases where there should be no interruption in therapy, three new drugs (eg, an aminoglycoside and two oral agents such as EMB and a fluoroquinolone) could be started until the transaminase concentration returns to less than two to three times the upper limit of normal (or to near baseline levels). Thereafter the first line medications can be restarted one at a time. RIF (perhaps together with EMB) should be restarted first. If there is no increase in AST after one week, PZA may be restarted[4].

Hepatic drug reactions usually occur in the first 2 months of treatment but may happen at any moment during the treatment period. Clinical, biochemical and histological features of ATDH are hard to distinguish from viral hepatitis. The signs and symptoms of liver injury are jaundice, abdominal pain, nausea, vomiting and asthenia. They are not specific enough to ascertain a liver disorder. Therefore, confirmation by laboratory liver testing is required. Complaints of ATDH are mostly relieved when treatment is interrupted. When treatment is not interrupted in time, ATDH can be fatal. The exact mechanism of ATDH is unknown. Isoniazid-induced hepatotoxicity is considered idiosyncratic[5]. Unpredictable or idiosyncratic reactions are adverse drug reactions that are not related to the pharmacological properties of the drug. Although they are dose dependent in susceptible individuals, they do not occur at any dose in most patients. Idiosyncratic reactions can affect any organ system, and include IgEmediated reactions as well as reactive metabolite syndromes. It is suggested that reactive metabolites, rather than the parent drug, areresponsible for most idiosyncratic drug reactions. Isoniazid-induced hepatotoxicity is not the result of a hypersensitivity or allergic reaction and is most probably caused by toxic metabolites[6].

Guidelines for management of ATDH have been published by the American Thoracic Society (ATS), the British Thoracic Society (BTS) and the Task Force of the European Respiratory Society, the WHO and the International Union Against Tuberculosis and Lung Disease. The management of ATDH depends on the supposed cause, therefore no unambiguous advice can be given. The hepatocellular pattern of liver injury, which is seen in isoniazid, rifampicin and pyrazinamide toxicity, has a predominant initial elevation of alanine aminotransferase. Therefore, this biochemical parameter is most often used to monitor the liver function during anti-tuberculosis treatment[7,8]. In summary, TB should be treated under supervision of a qualified physician. Patients should be advised to seek medical care if they experience any signs or symptoms of hepatotoxicity (i.e. jaundice malaise, nausea and vomiting). They should be advised not to drink alcohol during TB treatment. During treatment, the liver function only has to be monitored on a regular basis on indication (e.g. in patients with chronic liver disease or increased serum transaminases prior to treatment). In the case of signs or symptoms of hepatotoxicity, the liver function should be examined. In the case of confirmed moderate or severe drug-induced hepatotoxicity, treatment should be interrupted and reintroduced after the hepatotoxicity has resolved[9].

It is important to note that asymptomatic transaminase elevations occur in 20% of patients treated with standard antituberculosis regimens; prior to treatment or immediately after the start of treatment. Usually these elevations resolve spontaneously[10]. In many low-income countries, where the burden of TB is often high, liver function tests cannot be performed. In those situations one has to rely on clinical symptoms of hepatotoxicity,

such as jaundice, abdominal pain, nausea and vomiting[11]. The cause of hepatitis during TB treatment can either be the anti-tuberculosis drugs or something else, so the other possibilities have to be excluded before deciding that the hepatitis is drug induced. If moderate or severe ATDH is diagnosed (i.e. serum aminotransferase level >5 times the upper limit of normal [ULN] or >3 times the ULN with symptoms of hepatotoxicity), guidelines recommend to discontinue all drugs until liver function tests have become normal. When it is not possible to perform liver function tests, it is advisable to wait for an extra 2 weeks after the jaundice has disappeared before recommencing TB treatment. Once the ATDH has resolved, the same drugs are reintroduced consecutively[12,13].

Based on the above scenario, this descriptive case series study was designed to determine the frequency of derangement of liver enzymes in patients taking anti-tuberculosis therapy (ATT) within first 8 weeks of therapy.

MATERIALS AND METHODS

This descriptive case series study was conducted at the indoor and outdoor patients department of General Medicine, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan for blood sampling and biochemical assays. Total duration of study was 08 months. This study was performed on 117 human volunteers. Patients of both sexes, having age greater than 14 years and having normal liver enzymes at baseline were inducted in this study. Patients having known liver diseases, having a history of hepatitis, on drug (steroids and NSAIDs) therapies, history of obstructive jaundice, history of diabetes, anemia and other connective tissue disorders were excluded from the study.

Permission was taken from hospital ethical review committee. Informed written consent was taken from all patients. A detailed history including age, gender, occupation, contact history, duration of diagnosis of T.B, duration of taking ATT, history of co-morbid, type of medications taking, weight in Kg, nutritional status and organ involved was taken from the patients. Baseline LFTs was performed in every patient and repeated at 4 weeks interval x 2 times. To rule out lost follow up bias, contact numbers and addresses were taken from all the study cases. All liver function tests were performed within the hospital at baseline and re-tested at 04 and 08 weeks after start of ATT to reduce and to overcome technical bias from result of different laboratories.

STATISTICAL ANALYSIS

Data was entered and analyzed with help of statistical package for social sciences (SPSS ver 14). Descriptive statistics was used to calculate Mean and Standard Deviation for Quantitative variables i.e. age, weight (Kg), and dose of drug. Frequency with percentages were used for Qualitative variables such as gender, occupation, type of tuberculosis, duration of diagnosis of tuberculosis, duration of taking ATT, drug in use, and LFT's at 4 and 8 weeks.

RESULTS

Total of 117 fulfilled the inclusion criteria. 3 patients later on refused to participate in the study and were dropped. Rest of 114 patients were included in the study. Out of 114 patients, 71 were male and 43 were female. 12 patients had deranged LFTs while 102 patients had normal LFTs after 4 weeks of treatment as shown in figure 1. After 8 weeks of treatment with anti-tuberculosis therapy, 10 patients had deranged LFTs and 104 patients had normal LFTs as shown in figure 2.

When we compared LFTs after 4 weeks of treatment, it was found that 7 male patients and 5 female patients had deranged LFTs. While 64 male patients and 38 female patients had normal LFTs with non-significant p value of 0.498 as shown in table 1. After 8 weeks of treatment, 7 male and 3 female patients had deranged LFTs while 64 male and 40 female patients had normal LFTs with non-significant p value of 0.436 as shown in table II.

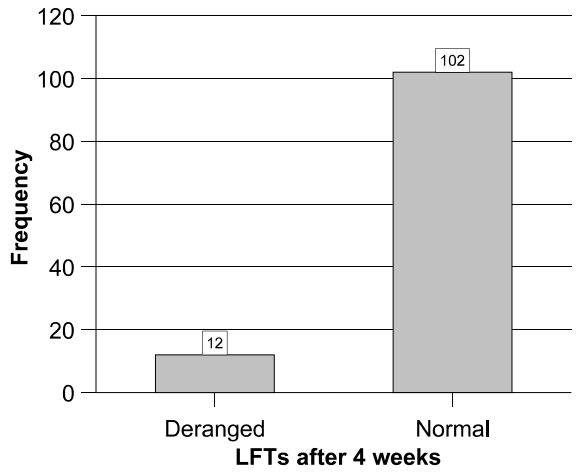

Figure-1. Frequency of LFTs derangement after 4 weeks.

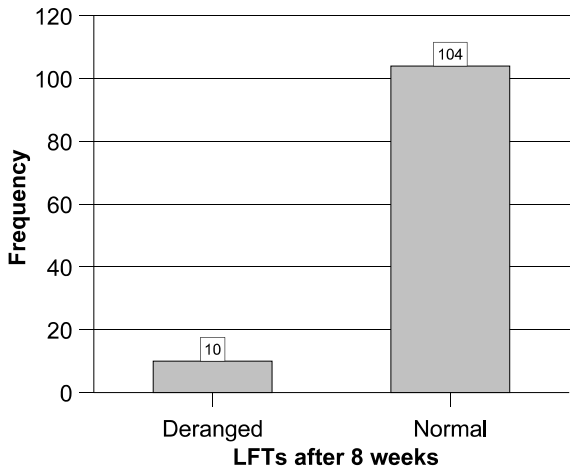

Figure-2. Frequency of LFTs derangement after 8 weeks.

LFTs Profile		Gender of patients		Total	P-value
		Male	Female		
LFTs after 4 weeks	Deranged	07 (58.3%)	05 (41.7%)	12 (100%)	0.498
	Normal	64 (62.7%)	38 (37.3%)	102 (100%)	
Total		71 (62.3%)	43 (37.7%)	114 (100%)	

Table-I. Comparison of LFTs derangement after 4 weeks in both genders.

** p<0.05 significant difference*

LFTs Profile		Gender of patients		Total	P-value
		Male	Female		
LFTs after 8 weeks	Deranged	07 (70.0%)	03 (30.0%)	10 (100%)	0.436
	Normal	64 (61.5%)	40 (38.5%)	104 (100%)	
Total		71 (62.3%)	43 (37.7%)	114 (100%)	

Table-II. Comparison of LFTs derangement after 8 weeks in both genders.

** p<0.05 significant difference*

DISCUSSION

Tuberculosis is a major cause of preventable infectious disease and death in the world. Timely diagnosis and proper chemotherapy are the mainstays of treatment. The hepatotoxic side effect of ATT has been under extensive discussion and studies to confirm their frequency and outcome in patients, all over the world. However, it is a surprising fact that most of this research work has been done in the west and in the more developed nations of the world, while studies to the effect have practically never, if ever been done in Pakistan; and especially the northern areas where Tuberculosis, remains a rampant killer to

date.

Incidence of LFTs derangement in our study was found to be 10.53% after 4 weeks of treatment and 8.77% after 8 weeks of treatment. When we compare the result of incidence of our study with the results of international studies, wide variations have been found in the incidence of hepatotoxic reactions during short course chemotherapy from different countries, with the reported incidence being 3 percent in the USA[14], 4 percent in the UK[14], 11 percent in Germany[15], 9.9 percent in Argentina[15], 13 percent in Hong Kong[16], 36 percent in Japan[17], 26 percent in Taiwan[17] and 8-36 percent in India[18]. The higher incidence of drug induced hepatitis in the Asian countries might be the result of ethnic susceptibility, inherent peculiarity of drug metabolism and/or the presence of various known risk factors such as HBV infection or malnutrition. Also, the lack of uniformity in the definition of drug induced hepatitis as well as in the use of different anti-TB regimens in different studies might be responsible for this difference.

In our study, gender difference was not significant ($p = 0.498$ and $p = 0.436$) for hepatotoxicity in both after 4 and 8 weeks respectively. Other studies had indicated that the female gender was a risk factor[19]. This is probably because almost two-thirds (62.28%) of our study population were males. Future studies must ensure an equal gender distribution in order to look at gender as a risk factor in our local population. Why only some patients who receive anti-TB drugs develop hepatitis is not clear. Several studies have searched for host factors, environmental factors or genetic factors such as HLA typing, cytochrome P450 2E120 or acetylator status. Several putative risk factors have been identified which lead to an increased risk of drug induced hepatitis.

Poor nutritional status has been considered to be one of the factors contributing to a higher incidence of drug induced hepatitis induced by short-course chemotherapy for TB in the developing countries. Drug metabolism pathways including acetylation pathways have been shown to be deranged in states of protein energy malnutrition[20].

Our present study has several merits. We included large number of patients. Such a large sample size has not been studied in previous Pakistani studies. Also, we carefully excluded patients with acute viral hepatitis by performing markers of acute viral hepatitis in all patients who developed features suggestive of drug induced hepatitis. Besides, we also excluded chronic alcoholics, patients with chronic liver disease and patients concomitantly consuming other hepatotoxic drugs as these conditions can produce changes mimicking drug induced hepatitis. As a result, pre-treatment serum AST, ALT and bilirubin were in the normal range. HIV infected patients were also excluded as these patients receive potentially hepatotoxic drugs and hepatitis in these patients may also be due to opportunistic infections.

CONCLUSIONS

Anti-tuberculosis drugs induced hepatotoxicity occurs less frequently usually reversible and rarely fulminant. All patients put on anti-tuberculosis therapy must be followed up for at least the initial 4 weeks, and the patient and caregivers should be told how to recognize signs of anti-tuberculous therapy (ATT) induced hepato-toxicity. The patients and the doctors have to be well educated about the adverse effects of the anti-tuberculous therapy (ATT), its early recognition and management.

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