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HEPATOTOXICITY IN ANTI-TUBERCULOSIS THERAPY: AN OBSERVATIONAL STUDY

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Abstract:

Objectives: *To determine the hepatotoxicity in patients receiving therapy against tuberculosis, determine the frequency & at which age chances of hepatotoxicity are more .And how to reduce these side effects.*

Methodology: *A randomized study was conducted on 100 patients in Tuberculosis Hospital, district headquarter hospital Jhang during July and August-2015. A questionnaire was designed to diagnose hepatotoxicity in patients undergoing tuberculosis therapy. As the important parameter for hepatotoxicity measurement is liver function test, so the major tests of liver function test were performed like, alanine aminotransferase, aspartate aminotransferase and bilirubin.*

Results: *Ratio of patients showing hepatotoxicity both males and females indicates that females are more hepatotoxic as compared to male. In the age range of 31-60 hepatotoxicity cases were more. The combination of two drugs isoniazid & rifampicin shows more hepatotoxicity.*

Conclusion: *It was concluded that the combination of isoniazd*
id & rifampicin showed more hepatotoxicity than combination with ofloxacin & pyrazinamide. Moreover, anti-tuberculosis therapy having ofloxacin in the absence of rifampicin was more efficacious.

Key Words: *Hepatotoxicity, Tuberculosis, Therapy*

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INTRODUCTION:

Tuberculosis (TB) is caused by Mycobacterium tuberculosis. It is estimated that over 8 million people contract tuberculosis each year, and approximately 2 to 3 million people die of this disease. In addition, it is thought that as many as 2 billion people have been exposed to the tuberculosis bacillus and are therefore at risk of developing active disease. This problem is further compounded by a dramatic increase in multidrug-resistant strains of *M.* tuberculosis [1]. Tuberculosis is associated with casemate necrosis, parenchymal lungs destruction and cavity formation. It is hypothesized that tuberculosis lung destruction is mediated at least in part by the precipitation of metalloproteinase released by mononuclear phagocytes [2]. TB is currently treated with a regimen of four drugs discovered before 1970: rifampin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (STR). These four drugs are administered for 2 months (the intensive phase), followed by the administration of rifampin and isoniazid for 4 to 7 months (the continuation phase), for a total of 6 to 9 months of treatment [3].

The patients which show resistance to the first line drugs are treated with second line drugs. These drugs include ofloxacin, ciprofloxacin which are the fluoroquinolone are effective in these cases. Here also resistance may develop so aminisyclic acid and ethionamide are also second line drugs. Other drugs cycloserine and pyridoxine are well tolerated. Like streptomycin some other injectables Amikacin, kanamycin and cepreomycin [4]. Major side effect of all drugs is hepatotoxicity. Others may include nausea or vomiting, jaundice-yellowish skin or eye, dark urine, unexplained fever or tiredness, tingling or numbness of hands or feet, or joint pains. Skin rashes, itching skin or bruising. Visual changes or change in red green color vision [5]. Liver function tests including alanine aminotransfrase (ALT), aspartate aminotransfrase (AST), alkaline phoaphatase (ALK.P),bilirubin are used to detect hepatotoxicity. The rise in these enzymes levels shows hepatotoxicity [6]. Liver injury was noticed within 15 days after start of therapy in a patient using four antituberculosis drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide).

Drug induced liver injury was a result of isoniazid due to the result of drug lymphocyte stimulation test [7]. Liver injury was a main adverse effect of anti-tuberculosis therapy. Metabolic process of these medications occurred in liver, there are increased chances of danger of liver injury in patients with chronic liver disease. Ofloxacin has activity against tuberculosis but it is eliminated through renal route [8]. Recognition of extremely high fever in 9 year old child who took rifampicin-isoniazid- ethambutol medications for the doubt of pleural tuberculosis, and was also taking glucurolactone and vitamin B6 for liver safety and to reduce neurotoxicity due to isoniazid. After taking anti-tuberculosis medications without isoniazid, extremely high slowly settled. Liver function of patient became normal after symptomatic therapy. In this way, extremely high fever which accompanied liver harm was due to isoniazid. It shows that extremely high fever that becomes visible during tuberculosis therapy was due to liver injury [9].

There is insufficiency of information on tuberculosis and anti-tuberculosis treatment cause liver injury in patients with long term liver disease. Tuberculosis other than lungs is frequent in patients suffering from liver disease & is frequent in children taking rifampicin & isoniazid medications together [10]. Gradual liver failure hardly noticed in tuberculosis chemoprophylaxis with isoniazid. Tuberculosis is the major complication for public health. Liver injury caused by Isoniazid is infrequent in mature person [11]. The purpose of this study was to determine the effectiveness & safeness of anti-tuberculosis therapy including oflaxacin, for patients having chronic liver disease.

METHODOLOGY:

A randomized study was conducted on patients in tuberculosis (TB) Hospital, district headquarter hospital(DHQ) Jhang Pakistan, during July-2015 to August- 2015.A questionnaire was designed to diagnose hepatotoxicity in patients undergoing TB therapy. As the important parameter for hepatotoxicity measurement is liver function test (LFT). So the major tests of LFT were performed like aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin.100 patients were included in this study. A convenient sampling technique was used. Both male and female TB patients were included in this study. Patients having different chest infections like pneumonia and asthma were excluded. A questionnaire was designed including information regarding patient demographic data, medications, liver toxicity, liver function test, normal values, patients values of liver function test & comorbid conditions such as disease, drugs, life style. Questionnaire was filled after checking the prescriptions & laboratory reports of patients by investigator. So the results of the major tests of LFT like AST, ALT and bilirubin were mentioned. Data was collected during 9:00am-1:00pm.Verbal consent was taken from the patients to participate in the study. Permission was taken from the Medical Superintendent to collect data from the hospital.

RESULTS:

A total of 100 patient participated, total males were 49 out of which 26 were hepatotoxic, while in case of females 51 were the cases out of which 29 showed hepatotoxicity in anti-tuberculosis therapy **(Table-1).** Hepatotoxicity with respect to age is depicted in **Table-2.** Results showed that the age range of 31-60 hepatotoxicity cases were more. Hepatotoxicity with respect to combination therapy is depicted in **Table-3.** The hepatotoxicity in case of RIF is more than INH, as the combination of two drugs INH & RIF shows more hepatotoxicity.

Table 1: Number of male and female patients and percentage hepatotoxicity

Total patients	Male			Female		
	total	hepatotoxic	% hepatotoxicity	total	Hepatotoxic	% Hepatotoxicity
100	49	26	53%	51	29	56%

Table 2: Hepatotoxicity cases with respect to age

N=100		
Age (years)	Total number of patients	Hepatotoxic patients
1-10	4	1
11-20	15	3
21-30	20	12
31-40	22	12
41-50	15	13
51-60	12	8
61-70	9	5
71-80	3	1

Table 3: Hepatotoxicity with respect to combination therapy

Drug combination	Total patients	Hepatotoxic patients	% hepatotoxic
a	10	3	30
b	16	7	43.7
a+b	31	17	54.83
a+b+c	16	16	62.5
a+b+c+d	27	18	66.66

'a' = INH, 'b'= RIF, 'c' = PZA, 'd' = EMB

DISCUSSION:

The hepatotoxicity is one of the most common adverse effects of tuberculosis treatment, varies from 1 to 10% in different countries. Depending on factors such as heritage, living condition and living area, the ratio was found to be maximum in India (8-10%) while lesser in Western countries being < 1% in US, 4% in UK, and 3.3% in Barcelona [12].

Reported risk factors for hepatotoxicity include older age, child age, female sex, poor nutritional status, high alcohol intake, pre-existing liver disease, hepatitis B carriage, hepatitis B and C infections, extensive disease, hypoalbuminaemia and acetylator status. In all disease groups, close follow-up is required during treatment with periodical clinical controls and laboratory tests.

Rifampicin was found to increase the chances of hepatotoxicity in individuals from 1.6%- 2.5% in a multidrug therapy. The pyrazinamide was also found to increase chances of hepatotoxicity [13].

Chances of hepatotoxicity were more in people greater than 40 than younger and increasing age also increases the chances of tuberculosis drug induced liver injury. However regression analysis showed that existence of additional disorders or diseases is the only risk factor associated with progression of hepatotoxicity. However, increasing chances of hepatotoxicity in older people may be due to increase in the presence of additional disorder or diseases as well as use of other medications. Women have more chances of developing hepatotoxicity than men [14].

Extended tuberculosis disease itself increases probabilities for tuberculosis drug induced liver injury, however it is not possible to eliminate other associated factors. In present study, hepatotoxicity was found to be more with extended disease instead of restricted disease (13% vs. 8.2%) [15].

It has been recommended that patients must be evaluated for hepatotoxicity via medical history, physical examination, laboratory analysis, and also should be acknowledged about hepatotoxicity, hepatitis symptoms including loss of appetite nausea/vomiting and abdominal pain and precautions for use of alcohol and hepatotoxic drugs. Routine follow up during treatment has been recommended only in patients with initially abnormal liver function tests and risk factors .Accordingly, follow up of patients based on clinical signs was considered to be sufficient by WHO and routine laboratory follow up was not recommended unless past history of liver disease, regular alcohol consumption or advanced was evident. In our study, laboratory controls were performed twice a week only in patients with initially high levels of liver enzymes while patients with normal laboratory findings lacking clinical complaints were not routinely followed in terms of laboratory.

While known to be hepatotoxic drugs, there is no consensus on indications for treatment withdrawal for INH, RIF and PZM. ATS recommended that if AST levels are more than five times the upper limit of normal even if without symptoms or more than three times the normal in the presence of symptoms, hepatotoxic drugs should be stopped immediately. According to BTS, if the liver enzymes were 5 fold of normal levels, all drugs should be discontinued.

In clinical practice, hepatotoxicity was considered in case of a rise of three times the upper limit of nomal levels of serum AST and /or ALT; a rise in the level of serum total bilirubin > 1.5 mg/dL or any increase in AST and/or ALT above pretreatment levels together with anorexia, nausea, vomiting and jaundice. Since which drug causes hepatotoxicity is unknown and alteration in treatment regime is quite likely due to drug resistance, treatment withdrawal included all of ongoing tuberculosis drugs in case of development of hepatotoxicity in our patients. According to recommendations, if the diagnosis is drug-induced hepatitis, the anti-tuberculosis drugs should be stopped and the drugs must be withheld until the normalization of the liver function tests. ATS recommends initiation of the new treatment regime following hepatotoxicity provided that ALT levels are below the two fold of upper normal limits. In our study population, treatment was re-initiated only after normalization of liver enzymes. In our clinical practice, we started the full drug dosages after the normalization of the enzyme values in 55 of 100 cases had recurrent hepatotoxicity.

Likewise, if patients with prolonged and severe hepatotoxicity tolerated RIF and INH, prolongation of treatment course to 9 months was reported to be a safer strategy than addition of PZM to treatment regime in ATS guideline. In WHO guideline, 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol has been suggested if rifampicin is implicated. If isoniazid cannot be used, 6-9 months of rifampicin, pyrazinamide and ethambutol has been indicated to be considered while if pyrazinamide is discontinued before the completion of the intensive phase, the total duration of isoniazid and discontinued before the completion of the intensive phase, the total duration of isoniazid and rifampicin therapy may be extended to 9 months.

In present study there is a combination therapy mostly used. The cases of hepatotoxicity were more in case of RIF as compared to INH. As the combination of drug increased from two to more hepatotoxicity chances increased. The data was collected at the patients who have duration of therapy

for maximum 2 months. There are some cases which show hepatotoxicity even with a short duration of treatment (15 days). The patients of every age were included most of the hepatotoxicity cases were seen at age of 40-60 years. These patients were not using any other drug. Only a single disease therapy was given to the patient .The only medication given as an adjunct therapy for dyspepsia which is the side effect of TB. It seems difficult to reach definitive conclusions regarding risks of individual regimens based on the use of multiple drug regimens in vastly different study populations with varying definitions of hepatotoxicity and different monitoring and reporting practices in the management of hepatotoxicity. As we cannot find which drug cause more hepatotoxicity because most of the treatment is done by combination therapy. In combination of 2, 3 and 4 the drugs are given to the patients. So it is concluded that there must be a close monitoring to Liver test while giving the TB medication to the patients.

CONCLUSION:

It was concluded that the combination of isoniazid & rifampicin showed more hepatotoxicity than combination with ofloxacin & pyrazinamide. Moreover, anti-tuberculosis therapy having ofloxacin in the absence of rifampicin was more efficacious.

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