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INCIDENCE AND RISK FACTORS FOR DRUG INDUCED HEPATOTOXICITY IN PULMONARY TB PATIENTS TAKING ATT ACCORDING TO DOTS

KEYWORDS: Drug induced hepatotoxicity, anti tubercular treatment, RNTCP

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ABSTRACT

INTRODUCTION: Tuberculosis still remains a serious clinical problem. Out of standard first line drugs, rifampicin and pyrazinamide have been observed to have hepatotoxic potential & drug induced hepatotoxicity (DIH) is an important and commonly encountered adverse effect with anti TB treatment [2,3]. A higher risk of hepatotoxicity has been reported in Indian patients [4-7] than in their western counterparts [7-9]. The reasons for the higher rate of hepatotoxicity in Indian patients are unclear.

AIMS AND OBJECTIVES: 1. To study the incidence of hepatotoxicity in patients receiving antitubercular treatment(ATT) as per Revised National TuberculosisControlProgramme.

2. To know the possible risk factors for the development of drug induced hepatotoxicity.

MATERIAL AND METHODS: In the prospective study, 100 freshly diagnosed pulmonary tuberculosis patients attending the medicine outpatient department or admitted in TMMC & RC, Moradabad and attending RNTCP DOTS center in the hospital were taken up for study.

RESULTS: TWO patient (2%) developed ATT induced DIH which included cases in the age group of 41-60years both patients had pretreatments albumin <3.5% gm/dl & BMI<17.5%

CONCLUSION: The incidence of asymptomatic elevation of liver enzymes secondary to ATT is 8% .Advanced age, BMI < 17.5, pretreatment hypoalbuminemia are predisposing factors for the development of ATT induced hepatotoxicity.

INTRODUCTION: Tuberculosis remains one of the world's serious clinical problems. Nearly 1/3rd of global population, is infected with M. tuberculosis and at risk of developing the disease. More than 90% of global TB cases and deaths occur in the developing world; more than 75% of cases are in the most economically productive age group (15-54 yrs).[1]. The essential services needed to control tuberculosis, based on diagnosis and treatment of infectious cases and incorporating the essential management tools, were developed and packaged as the DOTS strategy in the early 1990s. In 1993, W.H.O. took the unique step of declaring tuberculosis to be world emergency. With this in mind came the Revised National Tuberculosis Control Programme (RNTCP), which was pilot tested in 1993.The RNTCP is an application of the W.H.O recommended strategy of Directly Observed Therapy Short course (DOTS) in India. India now has the second largest DOTS Programme in the world. Presently regular first line drugs such as 'Isoniazid, Rifampicin, Pyrazinamide, Ethambutol' are essential components in DOTS strategy. Four drug regimen is able to cure almost all TB patients, although, anti-tuberculosis drugs have few side effects, one of commonly encountered is ATT induced hepatotoxicity (AIH)[4-7]

Early identification of ATT hepatotoxicity & its risk factors hold importance to stoppage of severe liver injury and prevent treatment failure. One of the reason for our failure to put halt to this TB epidemic is non compliance and interruption of ATT because of intolerable side effects of ATT. TB become challenge to treat when devlop adverse effect.[3-4]

. Several risk factors for the development of hepatotoxicity during short course therapy have been suggested. A higher risk of hepatotoxicity has been reported in Indian patients[5-8] than in their western counterparts[8-10]. The reasons for the higher rate of hepatotoxicity in Indian patients are unclear.

AIMS AND OBJECTIVES:

1. To study the incidence of hepatotoxicity in patients receiving antitubercular treatment as per Revised National Tuberculosis control Programme (RNTCP).
2. To know the possible risk factors for the development of drug induced hepatotoxicity

MATERIAL & METHODS: In the prospective study, 100 freshly diagnosed pulmonary tuberculosis patients males as well as females attending the medicine outpatient department or admitted in TMMC&RC, Moradabad and attending RNTCP DOTS center in the hospital were taken up for study.

INCLUSION CRITERIA:

- Patient diagnosed to have pulmonary tuberculosis with sputum smear positive for first time

EXCLUSION CRITERIA:

- Patient with Extra pulmonary TB
- Patient with pulmonary TB who are defaulters, treatment failure cases, & multi drug resistance cases
- Patient with abnormal baseline LFT
- Patient with cirrhosis of liver, acute viral hepatitis & /or gastro intestinal disease, renal, cardiac disease
- Patient refusing to give consent for study
- Patient with Alcohol dependence/Alcohol abuse.

STUDY AREA: Medicine outpatient & In patient department and attending RNTCP DOTS center in TMMC&RC, Moradabad.

METHODOLOGY: 100 patients with pulmonary tuberculosis diagnosed for the first time. Detailed history was taken & clinical examination & LFT determination was done in prospective study

RESULTS AND DISCUSSION: In our study, we enrolled 100 patients who are diagnosed to have pulmonary tuberculosis for the first time. These patients were given DOTS therapy as per RNTCP guidelines. All patients had normal liver function tests before the initiation of therapy. Liver function tests were monitored at 4th & 8th week of the treatment to note the elevation in serum bilirubin and liver transaminase levels which indicate the ATT induced hepatotoxicity. The results hereby are discussed under separate headings for each variable.

AGE: These results indicate that advancing age is an independent risk factor for drug induced hepatotoxicity consistent with previous reports.

BODY MASS INDEX: The body mass index can be independent

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factor to predict the risk of ATT induced liver damage. Both patients had BMI <17.5.

HYPOALBUMINEMIA: The patients presenting with pre-treatment hypoalbuminemia are more likely to have ATT induced liver damage than patients presenting with normal serum albumin levels.

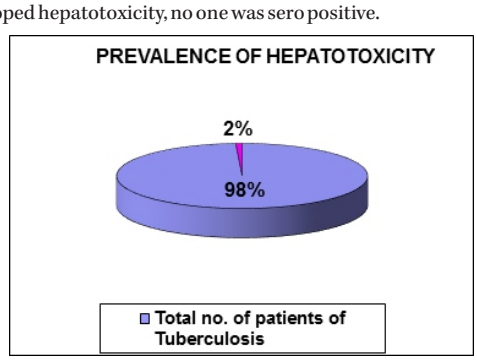
In this study 10 cases showed the evidence of antituberculosis treatment (ATT) induced liver damage in the form of elevation of serum bilirubin and transaminase levels above normal. Among these 2 cases developed overt drug induced hepatotoxicity (DIH) as defined above and remaining 8 cases had asymptomatic elevation of serum liver enzymes and bilirubin levels. The remaining 90 cases didn't show any significant change in their serum bilirubin and/or transaminase levels as compared to pre-treatment levels.

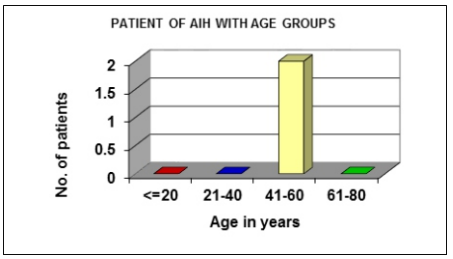
DISCUSSION: Isoniazid, rifampicin and pyrazinamide have been observed to have hepatotoxic potential and drug induced hepatotoxicity (DIH) is an important and commonly encountered adverse effect with anti TB treatment [2,3] Several types of drug induced liver damage have been described. Mechanisms of Drug Induced Hepatotoxicity include-Idiosyncratic damage, Dose dependent toxicity, Induction of hepatic enzymes, Drug induced acute hepatitis, Allergic reactions.

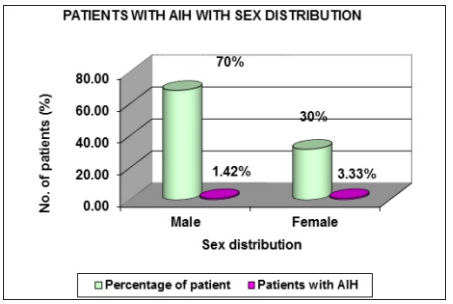
Specific Patterns of Hepatic Damage include- Disruption of intracellular calcium homeostasis, Cholestatic damage, Interruption of transport pumps and loss of villous processes, Reactions involving cytochrome p-450 system, Activation of apoptotic pathways and programmed cell death and Inhibition of mitochondrial function. So early recognition of risk factors with close follow up of patients receiving ATT and subjecting them to repeated liver function tests will significantly reduce morbidity and mortality and improve the compliance of the patients receiving ATT.

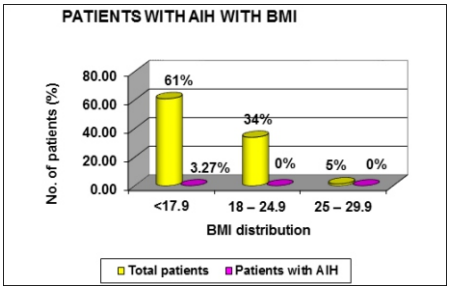
CONCLUSION:

ATT induced hepatotoxicity is one of the most prevalent drug induced liver injuries. Earlier recognition of AIH is needed to reduce significant morbidity and mortality.My study included a total of 100 patients suffering from pulmonary tuberculosis. 100 patients (70 male and 30 female) occurrence of hepatotoxicity in my study was 2% (2/100) which is on lower side compare to various International studies (2-36%). The maximum prevalence of toxicity (3.92%) was found in 41 -60 years age group. However, toxicity did not increase with increasing age as shown in various other studies. The prevalence of hepatotoxicity was found more in females than in males (3.33% vs 1.42% respectively). All the ATT induced hepatotoxicity occurred in patients having BMI <17.5 (3.27%). These 2 patients also had low serum albumin level. So it appears that low BMI and low serum albumin level which are pointers of under nutrition and poor socioeconomic status are risk factors for development of hepatotoxicity. Clinical parameters like nausea, vomiting, jaundice, ascites & edema are the main presenting features of drug induced liver disease. 8% (8/100) showed hepatic adaptation as evidenced by asymptomatic elevation of serum ALT which became normal even on continuation of therapy.In my study out of the 2 patients who developed hepatotoxicity, no one was sero positive.









Sl. No.	Name	HBs Ag	Anti IgM HBcAg	Anti HCV	IgM Anti HAV	IgM Anti HEV	HIV 1,2
33	BRAJLAL	-ve	-ve	-ve	-ve	-ve	Non-reactive
70	GAYATRIDEVI	-ve	-ve	-ve	-ve	-ve	Non-reactive

Sl. No.	Name	Age	Sex	DAY 0			DAY 30			DAY 60		
				T.B.	AST	ALT	T.B.	AST	ALT	T.B.	AST	ALT
33	BRAJLAL	60	M	1	22	26	4	400	424	2	55	68
70	GAYATRIDEVI	56	F	0.5	34	38	3.2	126	144	0.7	55	60

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