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Medicine

THE EFFECT OF ANTITUBERCULAR TREATMENT ON LIVER IN FRESHLY DIAGNOSED PULMONARY TUBERCULOSIS PATIENTS RECEIVING DOTS THERAPY

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ABSTRACT

OBJECTIVES: To study the incidence and factors involved in development of hepatic damage and overt hepatitis in patients receiving antitubercular treatment as per RNTCP (DOTS therapy-intermittent regimen)

Methods: In this prospective study, 100 freshly diagnosed pulmonary tuberculosis patients (67 males and 33 females) attending the Medical Clinic and DOTS Center were taken up for study and were given DOTS therapy as per RNTCP guidelines (cat I or III).

Results: The study group of 100 pulmonary tuberculosis patients consisted of 67 males and 33 females. Age varied from 15 – 80 years. Twenty eight patients (28%) developed antituberculosis treatment induced liver damage which included 23 (23%) patients who had asymptomatic elevation of liver enzymes and 5 (5%) patients who developed overt drug induced hepatotoxicity. 50% of cases in the age group of 51-60 years and 50% of cases in the age group of > 60 years developed drug induced liver damage.

Conclusion: The incidence of asymptomatic elevation of liver enzymes secondary to antituberculosis treatment is 23% and incidence of overt DIH is 5%. Advanced age, high alcohol intake, BMI < 18, radiologically severe disease and pretreatment hypoalbuminemia are predisposing factors for the development of ATT induced hepatotoxicity while sex is not factor. Peak incidence of hepatitis occurs in the first month of therapy.

KEYWORDS :

INTRODUCTION

Tuberculosis remains one of the world's deadliest diseases.The RNTCP is an application of the W.H.O recommended strategy of Directly Observed Therapy Short course (DOTS) in India. . Presently, standard first line drugs such as isoniazid, rifampicin, pyrazinamide, ethambutol or streptomycin are essential components of DOTS strategy. Of these, 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[4,5]. Identification of patients at increased risk for drug induced hepatotoxicity is important because hepatotoxicity causes significant morbidity and mortality and modification of the drug regimen may be required . Several risk factors for the development of hepatotoxicity during short course therapy have been suggested.some of them were: Advanced age ,female sex, extent of disease, hypoalbuminemia,malnutrition alcoholism underlying liver disease Acetylator phenotype N-Acetyl transferace activity Glutathione S-transferase. Genetic Factors :A higher risk of hepatotoxicity has been reported in Indian patients[6-9] than in their western counterparts. The reasons for the higher rate of hepatotoxicity in Indian patients are unclear. The cyp2e1 c1/c1 genotype remained an independent risk factor for hepatotoxicity suggesting that cyp2e1 genetic polymorphism may be associated with susceptibility to DIH caused by antituberculosis drugs. Age: Among infected persons, the incidence of tuberculosis is highest during late adolescence and early adulthood; the reasons are unclear. The incidence among women peaks at 25 to 34 years of age. The risk increases in elderly because of waning immunity and co-morbidity. Sex: In some studies, elderly females have been reported to be at a higher risk to develop ATT induced hepatotoxicity. However, some workers believe that the incidence of DIH due to ATT is not influenced by the sex of the patients[8].

Acetylator status: Studies by Sharma and associates showed that the hepatotoxic action of metabolites of INH is due to the hydrazine formed from INH. RIF induces the metabolism of INH by INH hydrolase resulting in the formation of isonicotinic acid and hydrazine. It has been suggested that concomitant administration of RIF and INH could result in increasing levels of hydrazine and this could provoke hepatotoxicity especially in slow acetylators. This hypothesis is supported by the finding of increased hepatotoxicity in slow acetylators[72].

N-Acetyl Transferase: Huang et al[73] reported that nat^2 slow acetylator status and age were the only independent risk factors for DIH due to ATT.

Underlying Chronic Liver Disease: Gronhagen-Riska et al[75] studied predisposing factors in hepatitis due to combined INH and RIF treatment and reported that one half of the patients who developed large increase in transaminases (>150 u/l) were either alcoholics or had a history of previous liver or biliary disease. The peak transaminase and bilirubin levels were higher in patients who were hep b virus carriers than in those who were not.

MATERIALS AND METHODS

Source of Data

In the prospective study, 100 freshly diagnosed pulmonary tuberculosis patients who came to general/pulmonary medicine out patient department of Rajiv Gandhi institute of medical sciences kadapa A.P an were taken up for study.Study Design: it is a prospective clinical study consisting of 100 freshly diagnosed pulmonary tuberculosis patients.they were undertaken to investigate the effect of anti tubercular drugs on liver with respect to elevation of liver enzymes and dih.Liver function tests were done before the initiation of therapy and repeated at 2nd, 4th, and 8th week of treatment.we have studied the relation of factors age,sex, alcohol intake,bmi and hypoalbuminia and severity of disease. we did not studied the risk factors like genetic factors and acetylator status. Inclusion Criteria Patients diagnosed to have pulmonary tubercul osis for the first time

Exclusion Criteria

1. Patients with extrapulmonary tuberculosis.
2. Patients of pulmonary tuberculosis who are defaulters, treatment failure cases and multidrug resistance cases.
3. Patients with abnormal baseline liver function tests.
4. Patients with cirrhosis of liver, acute viral hepatitis and/or gastrointestinal, renal or cardiac diseases.
5. Hepatomegaly due to any other causes.
6. HBsAg,HCV, positive cases.

OBSERVATION

In our study, we enrolled 100 patients who are diagnosed to have pulmonary tuberculosis for the first time. These patients were given DOTS therapy (cat I, cat III) as per RNTCP guidelines. All patients had normal liver function tests before the initiation of therapy. Liver function tests were monitored at 2nd, 4th and 8th week of the treatment to note the elevation in serum bilirubin and liver transaminase levels which indicate the antituberculosis treatment induced hepatotoxicity. The results hereby are discussed under separate headings for each variable.

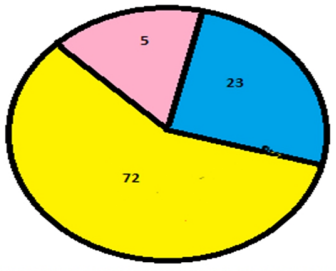
Antituberculosis treatment induced liver damage

In our study 28 (28%) 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 5 (5%) cases developed overt drug induced hepatotoxicity (DIH) as defined above and remaining 23 (23%) cases had asymptomatic elevation of serum liver enzymes and bilirubin levels.

The remaining 72 (72%) cases didn"t show any significant change in their serum bilirubin and/or transaminase levels as compared to pretreatment levels. Our findings are comparable with similar study done by Munir Ahmad Abbasi, Naseer Ahmed13 which considered 179 cases. Among these 23 (12.85%) cases developed drug induced liver damage, with 9 (18%) cases showing significantly elevated liver enzyme levels and 3 (6%) cases developing overt jaundice.

Table – 13 : Elevated Group

Enzymes	Number	%
DIH	5	5
Elevated liver enzyme cases	23	23.0
Non-elevated	72	72.0



DIH-5 ;ELEVATED LIVER ENZYME CASES-23 ;NON-ELEVATED-72

Table – 16 : Number of Patients With Liver Function Abnormality

Study Period	Serum Bilirubin (mg/dl)		AST (IU/L)		ALT (IU/L)		ALK (IU/L)	
	No	%	No	%	No	%	No	%
Baseline	-	-	-	-	-	-	-	-
Week 2	11	11.0	17	17.0	16	16.0	6	6.0
Week 4	20	20.0	28	28.0	27	27.0	7	7.0
Week 8	11	11.0	15	15.0	17	17.0	4	4.0

Chart – 9 : Percentage of patients with elevated enzymes & Bilirubin

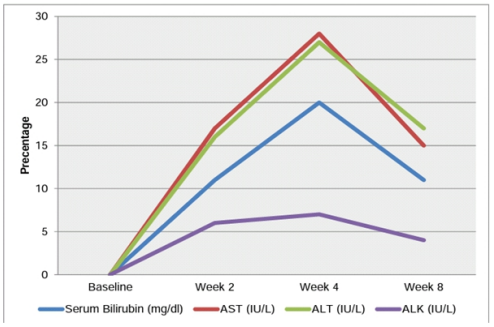


Table - 17 : Effect of Anti TB Drugs on Liver (n=100)

Study Period	Serum Bilirubin	AST	ALT	ALK
	(Mean + SD)	(Mean + SD)	(Mean + SD)	(Mean + SD)
Baseline	0.79+0.17	23.43+6.84	21.88+5.19	64.75+20.04
Week 2	0.87+0.22	33.76+19.96	34.24+26.11	73.86+32.72
Week 4	0.94+0.49	50.34+65.45	59.60+93.46	82.75+38.16
Week 8	0.88+0.29	37.68+20.97	36.74+24.54	76.53+24.44
Significance (Friedman Test)	0.176	P<0.001	P<0.001	P<0.001

Chart – 10 : Effect of Anti TB Drugs on Liver

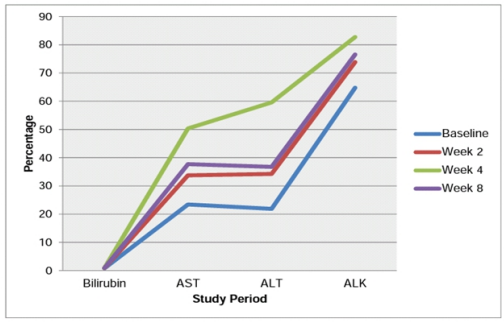
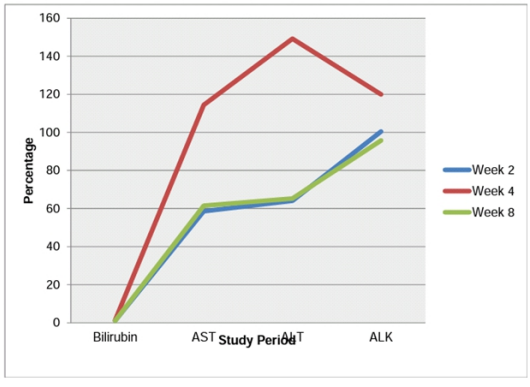


Table – 18 : Serum Bilirubin and Liver Enzymes in Elevated Group (N=28)

Study Period	Serum Bilirubin	AST	ALT	ALK
	(Mean+SD)	(Mean+SD)	(Mean+SD)	(Mean+SD)
Week 2	1.09+0.23	58.57+21.76	64.04+34.15	100.46+45.21
Week 4	1.38+0.72	114.36+97.37	149.21+142.67	119.96+47.65
Week 8	1.08+0.43	61.50+24.97	65.21+20.88	95.71+29.24
Significance				
(Friedman Test)	P<0.001	P<0.001	P<0.001	P<0.001

Chart – 11 : Liver Enzyme Levels in Elevated Group



Clinical Risk Factors for Development of Antituberculosis Treatment Induced Liver Damage The relatively higher incidence of hepatot oxicity in the developing countries has been attributed to various factors. There is no consensus as which one of these factors, whether alone or in combination is involved in the development of DIH and whether they could be used as markers to identify patients at high risk.

Age: In our study 1 (5%) case in the age group of < 20 years, 5 (22.7%) cases in the age group of 21-30 years, 6 (27.2%) cases in the age group of 31-40 years, 8 (34.7%) cases in the age group of 41-50 years, 4 (50%) cases in the age group of 51-60 years and 4 (80%) cases in the age group of > 60 years developed ATT induced liver damage. These

results indicate that advancing age is an independent risk factor for drug induced hepatotoxicity consistent with previous reports. The patients in the age group of > 50 years are 5.36 times more likely to have liver damage as compared to the patients in the age group of < 50 years (p=0.007).

Many studies have shown that advancing age is an independent predictor of ATT induced liver damage.

A study done by Munir Ahmad Abbasi, NaseerAhmed13 found that older age (OR=1.2) is a risk factor for DIH (p<0.05) as compared to non-DIH group.

Another study done by Hemant K. Khairnar15 found that hepatitis induced by ATT was more frequent in older patients (p<0.001). DIH due to INH prophylaxis has been more commonly observed with advancing age.

Riska et al48 found that the relative risk of hepatotoxicity due to INH prophylaxis was 2.8/1000 in patients younger than 35 years while it was 7.7/1000 in those >50 years of age.

Table – 14 : Association of Age with Drug Induced Liver Damage

Age in Years	Elevated Enzymes		Non-elevated Enzymes		Total
	No	%	No	%	No
Up to 20	1	3.6	19	26.4	20
21-30	5	17.9	17	23.6	22
31-40	6	21.4	16	22.2	22
41-50	8	28.6	15	20.8	23
51-60	4	14.3	4	5.6	8
>60	4	14.3	1	1.4	5
Total	**28**	**100.0**	**72**	**100.0**	**100**

Sex: In our study, among 23 (23%) patients who had asymptomatic elevation of liver enzymes, 18 (78.2%) cases were males and 5 (21.7%) were females. In DIH group, 4 (80%) cases were males and 1 (20%) were females.

Our study did not confirm previous studies suggesting that females are more likely to have DIH, as the other risk factors like advancing age, high alcohol intake, radio logically extensive disease were present significantly in males as confounding factors, giving an impression that liver damage is more common in males as compared to females.

High alcohol intake:In our study, 13 (46.4%) of 28 cases of elevated group had history of high alcohol intake (48 gm ethanol per day for more than a year) as compared to 11 (15.3%) cases in non-elevated group (n=72). So the patients with history of high alcohol intake are 4.46 times more likely to have elevated liver enzymes as compared to non-alcoholics while receiving ATT (p=0.005), (OR=4.81). Among non-alcoholics, sex is not a risk factor for elevation of liver enzymes. Our finding is consistent with previous studies. In a study by Hemant K. Khairnar15, the proportion of patients with a high alcohol intake was significantly higher amongst the DIH cases than the controls (19.8 Vs 4.9%) (p<0.001, OR=4.76).

In a study by Munir Ahmad Abbasi, Naseer Ahmed13 patients with DIH were more likely to have high alcohol intake (5% Vs 2%).The patients with high alcohol intake had three fold higher odds of developing hepatotoxicity. But, this difference was not statistically significant.

Body Mass Index: In our study, 14 (50%) cases in elevated group had BMI <18 as compared to 20 (27.8%) cases in control group (p=0.049, OR=2.42). So, the body mass index can be independent factor to predict the risk of ATT induced liver damage. The patients with BMI <18 are 2.42 times more likely to have elevated liver enzymes. Our findings are comparable with study done by SK Rajan et al21, who found that 9 (75%) of 11 cases of drug induced hepatitis had BMI <18. Similarly, Singh et al65 reported that malnutrition predisposed to the development of ATT induced hepatotoxicity. They also reported that malnourished patients had received higher than normal dosage of antituberculosis drugs per kg body weight especially under the programme conditions and suggested that this could be one of the reasons for the development of hepatotoxicity in them.

Severity of Disease:Patients with severe forms of tuberculosis have been reported to be at higher risk of developing hepatotoxicity than those with mild disease. We found that, 15 (53.6%) cases in elevated group had radio logically extensive disease as compared to 15 (20.8%) cases in the control group. So, the patients who present with radiologically severe disease are 4.38 times more likely to have drug induced liver damage than patients presenting with milder disease (p=0.001,OR=4.38). In DIH group (n=5) 4 (80%) cases had severe disease on their chest x-ray.Our results are consistent with similar study by Hemant K. Khairnar15 who observed that the disease extent was also a significant risk factor for the development of hepatitis, with 14% of the cases having extensive disease but only 3.5% of controls (p<0.001,OR=4.54). Four of the cases (4.6%) and six of the controls (1.5%) had military shadows on their radiographs. The presence of military tuberculosis was not associated with any increased risk for the development of hepatitis.Similarly in a study done by Munir Ahmad Abbasi, Naseer Ahmed13 50% of cases in DIH group had moderately/far advanced disease as compared to 33% in the non-DIH group (OR=2.0). But this difference was not statistically significant.

Hypoalbuminemia We observed that, 22 (78.6%) cases in elevated group (n=28) had pretreatment serum albumin < 3.5gm/dl as compared to 15 (20.8%) cases in non-elevated group (p<0.001, OR=13.93).In DIH group 4 (80%) cases had pretreatment serum albumin < 3.5gm/dl.So, the patients presenting with pretreatment hypoalbuminemia are 14 times more likely to have ATT induced liver damage than patients presenting with normal serum albumin levels. In a study byMunir Ahmad Abbasi, NaseerAhmed13, pretreatment serum albumin of <3.5gm/dl was present in 32% of DIH group compared with 16% of non-DIH group (p<0.01, OR=2.3). They concluded that patients with hypoalbuminemia had a two fold higher risk of developing DIH.In a study byHemant K. Khairnar1 the serum albumin was significantly lower in the cases during hepatitis than in the controls (p<0.001).there was no significant difference in the serum albumin among the patients with extensive or limited disease. The pretreatment serum albumin levels in the 35 cases in whom the results were available were lower than in the controls. But this difference was not significant.

TABLE – 20 : COMPARISON OF PREDICTIVE VALUES OF RISK FACTORS WITH RESPECT TO DRUG INDUCED LIVER DAMAGE

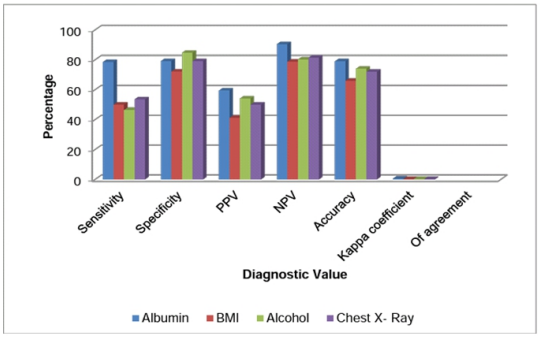
Diagnostic Value	Albumin	BMI	Alcohol	Chest X- Ray
Sensitivity	78.57	50.00	46.43	53.57
Specificity	79.17	72.22	84.72	79.17
PPV	59.46	41.18	54.17	50.00
NPV	90.48	78.79	80.26	81.43
Accuracy	79.00	66.00	74.00	72.00
Kappa coefficient Of agreement	0.53	0.21	0.33	0.32

Table – 15 : Association of Risk Factors with Drug Induced Liver Damage

Risk factors	Elevated Enzymes (n=28)		Non-Elevated Enzymes (n=72)		P value	OR (Elevated)
	No	%	No	%		
Male	22	78.6	45	62.5	0.125	2.20
Female	6	21.4	27	37.5	0.125	0.45
BMI <18	14	50.0	20	27.8	0.049	2.42

Alcohol	13	46.4	11	15.3	0.001	4.81
Chest X-ray						
(Severe)	15	53.6	15	20.8	0.001	4.38
Serum						
Albumin	22	78.6	15	20.8	0.000	13.93

Chart – 13 : Comparison of Risk Factors of Drug Induced Liver Damage



we did not study the other risk factors like genetic factors and acetylator status. This study excludes all patients of viral hepatitis during treatment, although the possibility that few of them had viral hepatitis that was not detected by the serological tests used cannot be excluded. Serological markers were evaluated for hepatitis A, B,C and E in all patients who showed abnormality in their liver functions. So, we could not comment on viral hepatitis as a risk factor for developing DIH in patients on ATT. Prospective studies on large number of patients receiving DOTS therapy are necessary to confirm our results.

CONCLUSION

The incidence of antituberculosis treatment (ATT) induced liver damage (includes asymptomatic elevation of liver enzymes and overt DIH) in patients on DOTS therapy is 28%. The incidence of drug induced hepatotoxicity (DIH) in patients receiving DOTS therapy (cat I & III) is 5%. The incidence of asymptomatic elevation of transaminases in patients receiving DOTS therapy is 23%. Peak incidence of ATT induced liver damage occurs at third and fourth week of therapy. Patients in the age group of >50 years are 5.36 times more likely to have drug induced liver damage than patients in the age group of <50 years.Male alcoholics are 4.46 times more likely to have drug induced liver damage as compared to male non-alcoholics.Patients with BMI <18 are 2.4 times more likely to develop ATT induced liver damage than patients with BMI >18. Patients with pretreatment hypoalbuminemia are 14 times more likely to have ATT induced liver damage. Advancing age, history of high alcohol intake, body mass index (BMI) <18, radiologically severe disease and pretreatment hypoalbuminemia are significant risk factors for the development of ATT induced liver damage while female sex is not a risk factor. Patients presenting with radiologically severe disease are 4.38 times more likely to develop ATT induced liver damage. Among all risk factors pretreatment hypoalbuminemia has more predictive value with respect to drug induced liver damage followed by high alcohol intake and radiologically severe disease. Among liver function tests serum bilirubin, alanine transaminase (ALT), aspartate transaminase (AST) levels increase proportionately with extent of drug induced liver damage. Alanine transaminase is good surrogate marker to assess the extent of liver damage.

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