Research Article

Incidence of hepatotoxicity in directly observed treatment short course

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ABSTRACT

Background: Antitubercular treatment induced hepatotoxicity usually has benign course, but may result in serious morbidity and even mortality. This study was undertaken to determine the incidence of hepatotoxicity in intermitted regimens directly observed treatment, short course (DOTS) and to evaluate the risk factors such as age, sex, nutritional status, disease extent, in the development of antitubercular drug induced hepatotoxicity in intermitted regimens (DOTS).

Methods: This was an observational study. All adults and adolescents above 15 years of age and weight more than 30 kilogramss, of either sex, on antitubercular treatment under intermitted regimens (DOTS), coming to chest and tuberculosis. Out-patient department of Dr. D.Y. Patil, hospital and research centre, Navi Mumbai, India, were included . Statistical analysis based on t- test done, predictability calculated to know the significance of study.

Results: 50 patients at random on intermitted regimens (DOTS) of antitubercular treatment. Majority (52%) were aged between 15-30 years. There were 24 (48%) males and 26 (52%) females. Serum bilirubin show a rise mean values between 2nd week (SD±053) p-value<0001(significant). Serum glutamic-pyruvic transaminase (SGPT) values show a rise in mean values between 2nd week (SD ±17.56) 4th week (SD±35.37) followed by fall in 6th week, p-value<001(significant), Serum glutamic-oxaloacetic transaminase (SGOT) value show a rise in mean values between 2nd week (SD±14.85) and 6th week (SD±26.18) followed by fall in 8th week, p-value<0001(significant). Mean serum albumin values show a rise in 2nd week (SD±0.53) and fall in the 4th week (SD±0.56) followed by a rise at 6th and 8th week, p-value<0001 (significant). Mean total protein value showed a fall from 2nd week (SD±1.16) to 8th week (SD±0.93) p-value<0001(significant).

Conclusions: Patients on antitubercular regimen should be educated about symptomatology related to hepatotoxicity, and they should be advised to consult the physician if symptoms occur. This will ensure reduction in dependency on repeated biochemical examination and also reduce patient's suffering.

Keywords: Antitubercular regimen, Hepatotoxicity

INTRODUCTION

Antitubercular treatment may result in adverse effects involving almost all systems in the body including the gastrointestinal tract, liver, skin, nervous system, oto-vestibular apparatus and the eyes. Of these, drug induced hepatotoxicity is an important and commonly encountered adverse effect.[1,2] Antitubercular treatment induced hepatotoxicity usually has benign course, but may result in serious morbidity and even mortality.[3] It is estimated that one third of the world's population is infected with *Mycobacterium tuberculosis*, resulting in 8.4 million new tuberculosis (TB) cases in the year 1999.[9]

Antitubercular therapy with rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin is very

effective, but the first three drugs are hepatotoxic. A higher risk of hepatotoxicity has been reported in Indian patients than in their western counterparts.[5-9] The risk of hepatotoxicity based on data from four prospective Indian studies, was 11.5% (95% confidence interval: 9.5-13.5) compared with 4.3% (95%: 3.4-5.3) in 14 published studies from west.[10] The reasons for this higher rate of hepatotoxicity in Indian patients are unclear.

Reported risk factors for hepatotoxicity include: older age, female sex, poor nutritional status, high alcohol intake, pre-existing liver disease, hepatitis B carriage, increased prevalence of viral hepatitis in developing countries, hypoalbuminemia and advanced tuberculosis, and inappropriate use of drugs and acetylator status.[11-21]

Early recognition of drug induced hepatotoxicity with immediate withdrawal of offending agent is very important to arrest its development and allow liver to heal.

British thoracic society suggested that if there is a rise in aspartate transaminase (AST) and/or alanine transaminase (ALT), AST to greater than 3 times normal, or a rise in bilirubin, or if the patient showed clinical symptoms of hepatitis then drugs should be stopped and reintroduced sequentially when these parameters fall to previous level.

After the serum transferase levels normalize and plateau, reinstitution of anti-tubercular therapy is done. It is a well-accepted fact that the risk of adverse effects must be balanced with the benefits of effective TB treatment. Prolonged interruption of treatment may lead to undesired drug resistance and may increase the duration of therapy.

Current American thoracic society centre for disease control recommends adequate monitoring (clinical as well as biochemical) of individuals in order to avoid unnecessary morbidity and mortality, hence decreasing the cost of illness. TB patients usually belong to poor socioeconomic status and they may not afford regular liver function tests. Close monitoring of the patient's physical conditions can be done in such situations.

Clinical rather than biochemical monitoring is used by many TB clinics, according to the study done by Leff and Leff.[22] With his background, this study was undertaken to determine the incidence of hepatotoxicity in intermitted regimens (DOTS) and to evaluate the risk factors such as age, sex, nutritional status, disease extent, in the development of antitubercular drug induced hepatotoxicity in intermitted regimens (DOTS).

METHODS

This was an observational study. All adults and adolescents above 15 years of age and weight more than 30 kilograms, of either sex, on antitubercular treatment under intermitted regimens (DOTS), coming to chest and tuberculosis, out-patient department of Padmashree Dr. D.Y. Patil, hospital and research centre, Navi Mumbai, India were included .

Patients of pulmonary or extra pulmonary, tuberculosis on antitubercular treatment in intermittent regimens (DOTS) and patients with abnormal baseline liver function test were excluded.

Study procedure

Patients of pulmonary or extra pulmonary tuberculosis were put on AKT as per DOTS categorization.

Category I: $2(HRZE)_3+4(HR)_3$
Category II: $2(HRZES)_3+1(HRZE)_3+1(HRE)_3$
Category III: $2(HRZ)_3 + 4(HR)_3$

H=Isoniazid, (dose=600 mg)
R=Rifampicin, (dose=450 mg)
Z=Pyrazinamide, (dose=1500 mg)
E=Ethambutol, (dose =1200 mg)

The numeral before a phase is the duration of that phase in months. The numeral in subscript is number of doses of that drug per week.

Table 1: Reference ranges used in liver function test.

Total bilirubin (mg/dl)	SGPT (u/l)	SGOT (u/l)	Alkaline phosphatase (u/l)	Total protein (gm/dl)	Serum albumin (gm/dl)
0-1	30-65	15-37	50-136	6.4-8.2	3.4-5.0

Base line liver function test was done. Informed consent was taken. Patients were clinically and biochemically monitored for hepatitis, monitored clinically throughout the treatment for nausea, vomiting, icterus, and pain in right hypochondrium. Patient monitored bio-chemically with liver function test before starting and after every 15 days in the 1st two months and as when needed.

Antitubercular treatment was stopped in case of three fold rise in upper value of normal range of serum transaminase. Reference ranges are shown in Table 1.

All 50 patients included in the study till the Completion of their AKT regimen and statistics maintained with final results.

Sample size

50 patients at random on intermitted regimens (DOTS) of antitubercular treatment.

Statistical analysis

Appropriate statistical representation method used to depict percentage wise occurrence of incidence of hepatitis and risk factors for hepatotoxicity.

Statistical analysis based on "t" test done, predictability calculated to know the significance of study.

RESULTS

29 (48%) patients were sputum positive while 31 (52%) were sputum negative.

Table 2: Distribution of cases.

Characteristics	No. of cases	Percentage
Age groups (in years)		
15-30	26	52
31-45	18	32
46-60	6	16
Sex		
Male	24	48%
Female	26	52%
BMI group		
	43	86%
	6	12%
	1	2%

Majority (52%) were aged between 15-30 years. There were 24 (48%) males and 26 (52%) females (Table 2).

Table 3: Variation in mean serum bilirubin according to time period.

Time period (weeks)	Range	Mean s. bilirirubin (mg/dl)	±SD
0	0.05-6.49	0.61	0.888
2	0.04-1.50	0.51	0.274
4	0.08-1.50	0.59	0.300
6	0.05-3.40	0.62	0.534
8	0.05-3.40	0.62	0.261

Serum bilirubin show a rise mean values between 2nd week (SD±053) p-value<0001(significant) (Table 3).

SGPT values show a rise in mean values between 2nd week (SD±17.56) 4th week (SD±35.37) followed by fall in 6th week (Table 4) p-value<001 (significant), SGOT value show a rise in mean values between 2nd week (SD±14.85) and 6th week (SD±26.18) followed by fall in 8th week (Table 5) p-value<0001(significant).

Table 4: Variation in SGPT according to time period.

Time period (weeks)	Range	Mean SGPT (u/l)	±SD
0	20.00-94.00	36.94	14.534
2	18.00-98.00	41.58	17.560
4	23.00-196.00	55.18	35.371
6	26.00-198.00	53.34	33.729
8	22.00-198.00	46.14	21.858

Table 5: Variation in SGOT according to time period.

Time period (weeks)	Range	Mean SGOT (U/L)	±SD
0	17.00-118.00	34.38	18.746
2	13.00-111.00	34.06	14.858
4	19.00-120.00	42.18	24.899
6	15.00-123.00	45.26	26.188
8	17.00-120.00	38.32	20.502

Table 6: Variation in mean serum albumin according to time period.

Time period (weeks)	Range	Mean s. albumin (gm/dl)	±SD
0	2.10-4.80	3.68	0.612
2	2.90-4.90	3.76	0.538
4	2.10-4.60	3.61	0.563
6	2.20-4.90	3.70	0.530
8	2.80-4.90	3.78	0.522

Table 7: Variation in t. protein according to time period.

Time period (weeks)	Range	Mean t. protein (gm/dl)	±SD
0	3.30-103.00	10.39	13.438
2	5.80-10.40	8.61	1.163
4	5.90-10.20	8.46	1.061
6	5.90-10.10	8.46	1.014
8	5.50-10.20	8.41	0.931

Table 8: Distribution of site disease.

Site of disease	No. of cases	Percentage (%)
EP- abdominal TB	1	2
EP- axillary LN	1	2
EP-cervical LN	13	26
EP-hydro-pneumothorax	1	2
EP-pl. Eff	8	16
EP-milliary TB	2	4
EP-TB salpingitis	1	2
Ep- tb wrist joint	1	2
Pul. TB	21	42
Pul. TB with lt pul. Eff	1	2

Table 9: Statistical analysis of liver function test values according to time period.

Time period (weeks)	t-values of variable					P value	Remarks
	Serum bilirubin	SGPT	SGOT	Serum albumin	Total protein		
2	12.95	16.74	16.21	49.45	52.31	<0.0001	Significant
4	12.82	11.03	11.98	45.28	56.37	<0.0001	Significant
6	8.52	11.18	12.22	49.36	59.04	<0.0001	Significant
8	7.95	14.93	13.22	51.25	63.84	<0.0001	Significant

Mean serum albumin values show a rise in 2nd week (SD±0.53) and fall in the 4th week (SD±0.56) followed by a rise at 6th and 8th week, p-value<0001 (significant) (Table 6). Mean total protein value showed a fall from 2nd week (SD±1.16) to 8th week (SD±0.93) (Table 7) p-value<0001 (significant).

DISCUSSION

This study was done to know the incidence of hepatotoxicity in patients on antitubercular drugs under intermittent regimens (DOTS) and evaluation of risk factors causing hepatotoxicity. It comprised of 50 patients, diagnosed with tuberculosis (both pulmonary and extra pulmonary).

Antitubercular treatment induced hepatotoxicity usually has benign course but may result in serious consequences including death.[3] Treatment for tuberculosis with rifampicin, isoniazid, pyrazinamide and ethambutol is very effective but first three of these drugs have been shown to hepatotoxic in varying degrees.

Isoniazid hepatotoxicity is mostly acute hepatocellular in type, through a mixed hepatocellular-cholestatic has been reported. Concomitant use of rifampicin leads to earlier and more frequent hepatotoxicity, some in less than ten days.

A study done at University, department of medicine and microbiology, Royal Free School of Medicine, London, UK, suggested, symptomatic liver disease occurs less commonly, being reported in 0.5% to 3%.

Another meta-analysis by Steels MA revealed a clinical hepatitis rate of 0.6% when isoniazid was used alone, and 1.6% and 3% when used in multidrug regimen, not including rifampicin.[12]

Pharmacological studies of rifampicin given as a single agent show that serum bilirubin values may be transiently elevated about three hours after a single dose, returning to normal within 24 hours.[23,24] This meta-analysis included several small, uncontrolled clinical studies in adults reported transaminase elevations and occasional cases of overt clinical hepatitis during rifampicin therapy in absence of isoniazid.

When these studies were pooled, the mean incidence of hepatotoxicity was 1.1%, lower than seen with isoniazid plus rifampicin therapy i.e. 2.5%.[12] All these studies were done with daily treatment regimens.

Pyrazinamide was shown to cause overt hepatitis in 8%. Experiences with lower dose regimens, in combination with other agents, suggest that is only a small risk of hepatocellular injury, though cases of fatal hepatic necrosis have been described.

According to a study conducted at New Delhi, India, Tuberculosis centre the incidence of hepatotoxicity during DOTS therapy was observed to be only 1 out of 1195 patients, while in Hong Kong study 2% of patients were reported to have hepatitis.[25,26] A study by Anand et al to know risk factors of hepatotoxicity during antitubercular treatment in daily regimen showed incidence of 10.1%.[27]

Our study shows incidence of hepatotoxicity of 2% (p-value<001) (1 patient out of 50) under intermittent regimens (DOTS), when considering derangement of hepatic enzymes three fold of normal upper limit.

The derangement (in case no. 2) was observed in between 2 weeks and 6 weeks with symptoms of nausea, vomiting and abdominal pain. Antitubercular drugs were stopped and patient observed. Liver function test repeated after one week of stopping treatment which showed a significant decrease in level of enzymes, which was self-limiting, antitubercular drugs were re-introduced, patient completed treatment and remained asymptomatic then after.

Varied results were observed when age was correlated with hepatotoxicity by many studies. A study done by Stead et al suggested liver damage increases with age, he observed isoniazid induced hepatotoxicity in 4.5% of 2,000 of elderly patients.[28] Pande et al observed it to be more frequent in older patient.[19] Mahmood K et al in another study suggested advancing age a risk factor.[29]

While another study in Nepalese population by Shakya et al found it to be higher in younger patients.[30] While some Indian studies suggested no correlation.

In our study 16% of patients were in age group of 40-60 and 52% of patients in age group of 15-30. Both the groups did not show any correlation with hepatotoxicity.

Female sex has been reported to be at higher risk of developing antitubercular induced hepatotoxicity. A study at Karachi by Khalid et al compared the percentage of hepatotoxicity and found it in 26.3% of females and 19.7% in males.[31] A study in Nepal by Shakya et al, proved female gender an independent factor for antitubercular drug induced hepatotoxicity.[32] In our study 58% patients were females and none of them showed features of hepatotoxicity either in terms of symptomatology or in terms of liver function test.

Malnutrition and hypoalbuminemia have been shown in some studies to be a risk factor for hepatotoxicity, Mehta et al showed drug acetylation and metabolising process deranged in protein energy malnutrition.[33] Study by Sharma et al at AIIMS, New Delhi, India suggested two fold risks.[34] On the other hand Anand et al showed no role of malnutrition and hypoalbuminemia as a risk factor as long as drug doses are correctly delivered per kg body weight.[35]

In our study results showed 86% of patients with body mass index (BMI) ranging between 15-20 and 12% between 21 to 25. Low BMI has not been found to be a cause of drug induced hepatotoxicity. Unlike other regimens, right dosages under DOTS may be a reason BMI for not developing hepatotoxicity.

Extensiveness of the disease was described as a risk factor by Shakya et al for hepatotoxicity.[32] According to his study, sputum positive had moderately advanced TB infections. A study at civil hospital, Karachi, Pakistan showed 59% of patients with sputum status severely affected. In our study 48% patients were found to be sputum positive but did not develop hepatotoxicity due to antitubercular drugs.[31]

Biochemical monitoring is not replacement for close clinical monitoring. Clinical heterogeneity dictates that each case should be assessed individually with the monitoring procedure tailored accordingly.

More frequent and intensive biochemical monitoring may be indicated in situations where the patient's condition or the liver enzyme levels change rapidly. If the antitubercular drugs are given for the treatment of latent TB infection, the standard for safety monitoring is clearly higher than that the treatment of active disease.[36]

Not uncommonly, mildly elevated pre-treatment liver enzymes are encountered among TB patients without any other evidence of liver disease. When these patients are given the full treatment regimen, their enzyme levels are often observed to revert to normal.[37]

In our study liver function tests were done pretreatment followed by every fifteen days for two months. There occurred a rise in serum transaminase level between 2nd week and 6th week of starting treatment; this rise in transaminase levels did not require treatment cessation.

If significant drug-induced hepatitis occurs, careful balance of all factors is required to decide on when and how to resume treatment. It should be noted that patients with active TB disease would develop detrimental consequences, if the TB is left untreated, particularly if the disease is extensive. Hence, the decision on when to resume treatment with anti-TB drugs should be made not only by the time the liver function tests reverting to the normal or pretreatment level, but also on the rate of TB disease progression and the disease severity.

Sometimes, a regimen with less hepatotoxic drugs or a combination of drugs without potential hepatotoxicity may have to be tried first, with the more potent but potentially hepatotoxicity drugs added subsequently one after the other. It is generally desirable to include both isoniazid and rifampicin in the final regimen whenever possible so that the duration of treatment does not need to be excessively prolonged.

During resumption of the treatment, the liver chemistry should be closely monitored, and the frequency of monitoring usually depends on the severity of the liver dysfunction that has had occurred and the drugs in trail. It has to be noted that the cause of that hepatitis, apart from being drug-induced, could be due to alternative such as viral infections, or induction by other drugs used at the same time. Resumption of treatment utilizing the original full drug regimen may rarely be possible.

Although there has been substantial progress in the treatment of certain liver disease, like chronic viral hepatitis, the implications of these advances on the treatment of tuberculosis have not yet been fully clarified.

The above discussion and findings suggest, delivery of correct dosages of antitubercular drugs per kilogram body weight should be ensured. Dosages under DOTS regimens are supervised, and total amount of dosages per work given is less than that compared to dosages in daily regimen hence chances of hepatotoxicity can be reduced, timely clinical & biochemical evaluation should also be done to avert the risk of hepatotoxicity.

In our study one patient out of 50 developed hepatotoxicity (i.e. incidence of 2%). The criteria used in this study was as suggested by British Thoracic Society (i.e. rise in SGPT and/or SGOT greater than three times normal, or a rise in bilirubin, or if the patient showed symptoms of hepatitis then drug should be stopped). In a study conducted at New Delhi Tuberculosis Centre, India, incidence of hepatotoxicity during DOTS therapy was observed to be only 1 out of 1195 cases, while in Hong Kong study 2% of patients were reported to have

hepatitis, criteria used in this study was as per recommendations by CDC-US which suggested stopping ATT if SGOT/SGPT are raised more than five times the upper normal limit.[38-40]

Our study showed incidence of 2%, while considering a three-fold rise in SGPT and SGOT levels of the upper limit and presence of symptoms of hepatotoxicity which when compared to daily regimen is very much low.

Last but not least patient's awareness is equally important, patients on antitubercular regimen should be educated about symptomatology related to hepatotoxicity, and they should be advised to consult the physician if symptoms occur. This will ensure reduction in dependency on repeated biochemical examination and also reduce patient's suffering.

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