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Study of Hepatotoxicity During Antitubercular Therapy in Children

Dr. Sushil Kumar[1], Dr. Chand Miyan Kamaal[2*], Dr. Mohd. Anjoom[3], Dr. Neetu Goyal[4]
[1]Assistant Professor, Department of Pediatrics, Shaikh-Ul-Hind Maulana Mahmood Hasan Medical College, Saharanpur 247001, Uttar Pradesh, India
[2]Associate Professor, Department of Pharmacology and Therapeutics, Shaikh-Ul-Hind Maulana Mahmood Hasan Medical College, Saharanpur 247001, Uttar Pradesh, India
[3]Assistant Professor, Department of Pharmacology and Therapeutics, Shaikh-Ul-Hind Maulana Mahmood Hasan Medical College, Saharanpur 247001, Uttar Pradesh, India
[4]Assistant Professor, Department of Pathology, Shaikh-Ul-Hind Maulana Mahmood Hasan Medical College, Saharanpur 247001, Uttar Pradesh, India

Original Research Article

***Corresponding author**
Dr. Chand Miyan Kamaal

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Abstract: All pharmacological interventions balance efficacy and toxicity; there are few efficacious agents that do not have some toxicity risk. In the case of antituberculosis agents the major risk is hepatotoxicity and three agents identified by World Health Organization (WHO) as essential, isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA), carry such a risk. The liver is vulnerable to injury from the first line anti-tuberculosis drugs. This may result in mortality, long term morbidity and reduced compliance to therapy. A prospective study of 100 cases was done in this study. The cases were divided into two broad groups. Group A comprised control of 25 children and Group B comprised different varieties of tuberculosis patient with 75 children. Serial estimations of SGPT and alkaline phosphatase were undertaken at the beginning of therapy and at 1st, 2nd, 3rd, 4th, 5th, 6h, 8th, 10th and 12th weeks of antitubercular therapy**.** Out of 75 patients studied 49 cases were male (65.3%) and rest were female (34.7%). Out of 75 patients examined, 33.3% had primary complex and 20% tuberculous pneumonia, 5.4% lymphadenopathy, and 4% had Koch's abdomen. In group I none developed hepatomegaly and jaundice; while in Gr. II 2 patients (6.2%) and Gr. III 3 patients (11%) had developed clinical jaundice and hepatomegaly. The highest incidence of hepatic dysfunction in 2m-1 yr of age group 42.8% followed by 31.25% in 1-3yrs age group, 37.03% in 3-6 yrs and 285 in 6-12 yrs age group. There was no symptomatic case of hepatic dysfunction in 1st 2 weeks. Between 2-5 wks after initiation of ATT only 2 patients had symptomatic liver dysfunction. After 5 wks of starting treatment 3 patients had developed symptomatic hepatic dysfunction. Overall hepatotoxicity in our study was 33.33%. Maximum toxicity occurred after only 2 weeks of ATT. There was inverse correlation of toxicity with the age of patient. There was direct correlation of severity of malnutrition to toxicity of ATT in the study cases.

Keywords: Hepatotoxicity, clinical jaundice, antitubercular drugs, children, causality, drug-induced.

INTRODUCTION

The spectrum of hepatic dysfunction ranges from mild elevation of serum transaminase in symptomatic patients to severe hepatocellular necrosis. Elevated transaminase values arevfrequent during 1st few weeks of therapy. There are usually no symptoms and levels subside despite continuing INH. Mild elevation of trasnaminase is usually self limiting fatal cases are unusual. These adverse reactions usually ensue within first 3 months of starting the therapy. Drug-induced hepatitis is vastly unrecognized and underreported, such that the true incidence is unknown [1, 2].

Elevated transaminases or alkaline phosphatase alone without jaundice or hyperbilirubinemia qualifies as mild disease. Elevated liver enzymes without symptoms may be part of an adaptation process especially when transaminases are less than 5 × ULN (upper limit of normal). Presence of hyperbilirubinemia with a bilirubin of >2 mg/dl qualifies as moderately severe disease. Presence of prolonged international normalized ratio (>1.5),

encephalopathy or ascites with or without hospitalization accompanied by hyperbilirubinemia or jaundice connotes severe disease. Mortality in the latter category varies depending on the exposed drug, being 21% for antituberculosis drug-induced liver injury [9] and 9–17% in non-tuberculosis drug-induced liver injury [1, 3-6].

Impairment in liver functions can be assessed by investigations like serum bilirubin, transaminases, alkaline phosphatase and serum protein. Transaminase and alkaline phosphatase are very important investigation for early detection of adverse reaction. Routine screening should be done before treatment is started and at 2^{nd} week, 4^{th} week and later. This screening helps in prevention of severe hepatic damage. Most of the toxicity of ATT has been reported with reference to adults [7]. The study in children about the hepatotoxicity of these drugs is very limited. So this study has been undertaken to know the impairment of liver function with the drugs either alone or in combination while on treatment for tuberculosis.

AIMS & OBJECTIVES

Study was done to identify children developing asymptomatic or sysmptomatic hepatic dysfunction during antitubercular therapy. It also revealed hepatotoxic effects of different antitubercular drug regimens in children and its relationship with nutritional status of the child.

MATERIALS & METHODS

The cases for the present study were selected from the Department of Paediatrics, LLR & Associated Hospitals, GSVM Medical College, Kanpur, during the period from Feb 2006 to Nov. 2007. Seventy five children affected from various types of tuberculosis were taken for the study. Twenty five children who were not affected from TB were taken as control. Demographic, general and clinical information were noted. Routine blood and urine examination findings were noted. X-ray was done in all cases. Serum bilirubin measured by modified diazo method in all cases and controls. Serum glutamic pyruvate transaminase (SGPT) and serum alkaline phosphatase were measured in every case.

The patients were categorized into three groups according to drugs they were taking with potential toxicity to liver.

Group I: Patients receiving INH alone
Group II: Patients receiving INH + Rifampicin
Group III: Patients receiving INH+ Rifampicin+ Pyrazinamide

Addition of streptomycin and/or ethambutol was allowed in any of the above groups as their hepatotoxicity is not significant. Serial estimations of SGPT and alkaline phosphatase were undertaken at the beginning of therapy and at 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 5^{th}, 6^{th}, 8^{th}, 10^{th} and 12^{th} weeks of antitubercular therapy. Weekly estimation of serum enzymes were undertaken in those cases with symptomatic or asymptomatic liver dysfunction for atleast 10 weeks. Elevation of serum glutamic pyruvate transaminase more than the mean value was taken as the symptomatic liver dysfunction. The patients were periodically examined for hepatomegaly and jaundice. The estimation of SGPT was done with the help of SGPT (ALT) reagent kit made by Span diagnostic kit private limited by colorimetric method. In this study estimation of serum ALT was undertaken with method based upon of Reitman and Frankel. Pyruvate formed in the process coupled with 2,4 Dinitrophenyl hydrazine to give the corresponding hydrazone, which gives brown color in alkaline medium and this can be measured colorimetric. The magnitude of aminotransferase alteration can be classified as “mild” (< 5 times the upper reference limit), “moderate” (5–10 times the upper reference limit) or “marked” (> 10 times the upper reference limit). This classification is somewhat arbitrary, since no uniform definition exists and various reviews of the subject use different cut-off points [8].

RESULTS

A prospective study of 100 cases was done in this study. The cases were divided into two broad groups. Group A comprised control of 25 children and Group B comprised different varieties of tuberculosis patient with 75 children. In Group a serum glutamic pyruvic transaminase and alkaline phosphatase levels were matched.

Table-1: Showing age distribution and mean value of SGPT in control cases

Age group	No. of cases	Serum SGPT (IU/ml)	
		Range	Mean
2 m- 1 yr	3	8-19	13.67
1-3 yrs	8	7-15	10.63
3-6 yrs	5	6-15	10.86
6-12 yrs	9	4-21	13.50

Table-2: Age and sex wise distribution of study group

Age group	No. of cases	Percentage
2 m-1 yr	7	9.4
2-3 yrs	16	21.3
3-6 yrs	27	36
6-12 yrs	25	33.3
Sex		
Male	49	65.3
Female	26	34.7
Total	75	100

Table 2 shows 36% of the patients belonged to preschool age group followed by 33.3% of school going age, 21.3% of toddler and 9.4% of infants among study group patients. Out of 75 patients studied 49 cases were male (65.3%) and rest were female (34.7%).

Table-3: Distribution of types of TB cases in study group

Types of TB	No. of cases	Percentage
TB meningitis	27	36
Primary complex	25	33.3
Tubercular pneumonia	15	20
TB lymphadenopathy	4	5.4
TB abdomen	3	4
Chemoprophylaxis	1	1.3
Total	75	100

The above table 3 shows that out of 75 patients examined, 33.3% had primary complex and 20% tuberculous pneumonia, 5.4% lymphadenopathy, and 4% had Koch's abdomen.

The table 4 shows that Gr. I consisted of 21.3% of total patients followed by Gr. II 42.7% and Gr. III 36%.

Table-4: Distribution of patients studied in different drugs combination

Group with drug combination	No. of cases	Percentage
Group I (HE/S)	16	21.3
Group II (HR & or S or E)	32	42.7
Group III (HRZS & or E)	27	36
Total	75	100

Table-5: Incidence of clinical hepatic involvement during antituberculous therapy

Group	No. of patients	Hepatomegaly & Jaundice	Percentage
I	16	Nil	0
II	32	2	6.2
III	27	3	11

This table 5 shows that in group I none developed hepatomegaly and jaundice; while in Gr. II 2 patients (6.2%) and Gr. III 3 patients (11%) had developed clinical jaundice and hepatomegaly.

Table-6: Comparison of serum SGPT in cases and control

Group	No. of patients	Only elevated enzyme level	Range IU/ml	Mean IU/ml	P value
Control	25	Nil	10.6-13.6	12.04	
I	16	3	26-45	34	
II	32	9	30-105	59.6	
III	27	8	26-120	51	

Above table 6 shows that in control group none of the cases had elevated SGPT level. There was mild elevation of SGPT in Gr. I while in Gr. II & III there was more than 2 fold rise in SGPT levels.

Table-7: Incidence of hepatic dysfunction among study patients group

Group	No. of cases	Jaundice & hepatomegaly	Only elevated enzyme level	Total cases of hepatic dysfunction	%
I	16	Nil	3	3	18.75
II	32	2	9	11	34.3
III	27	3	8	11	40.7
Total	75	5	20	25	33.33

Table 7 shows that in Gr. I 3 patients had asymptomatic hepatic dysfunction, whereas 9 patients in Gr. II and 8 patients in Gr. III had asymptomatic hepatic dysfunction.

Table-8: Interval between onset of therapy and hepatomegaly

Time interval	No. of cases	Toxicity				
		Symptomatic	Asymptomatic	Gr. I	Gr. II	Gr. III
0-2 weeks	5	-	5	-	3	2
2-5 wks	12	2	10	2	6	4
5-12 wks	8	3	5	1	2	5
Total	25	5	20	3	11	11

Table 8 shows there was no symptomatic case of hepatic dysfunction in 1st 2 weeks. Between 2-5 wks after initiation of ATT only 2 patients had symptomatic liver dysfunction. After 5 wks of starting treatment 3 patients had developed symptomatic hepatic dysfunction.

Table-9: Hepatic dysfunction according to age of the patients

Age group/ Study group	2 m- 1 yr [n=7]		1-3 yrs [n=16]		3-6 yrs [n=27]		6-12 yrs [n=25]	
	Hepato-toxicity	%	Hepato-toxicity	%	Hepato-toxicity	%	Hepato-toxicity	%
I	Nil	0	Nil	0	2	7.4	1	4
II	1	14	3	18.75	4	14.8	3	12
III	2	28.5	2	12.5	4	14.8	3	12
Total	3	42.8	5	31.25	10	37	7	28

The above table 9 shows that highest incidence of hepatic dysfunction in 2m-1 yr of age group 42.8% followed by 31.25% in 1-3yrs age group, 37.03% in 3-6 yrs and 285 in 6-12 yrs age group.

Table-10: Hepatotoxicity versus nutritional status [NS]

NS	Group I			Group II			Group III		
	No. of cases	Toxicity	%	No. of cases	Toxicity	%	No. of cases	Toxicity	%
Normal	4	0	0	5	1	20	4	1	25
Mild-moderate PEM	9	2	22	22	9	40.9	17	7	41.57
Severe PEM	3	1	33.3	5	1	20	6	3	50
Total	16	3	18.75	32	11	34.3	27	11	40.7

Above table 10 shows that in group I there was 18.75% cases of mild to severe PEM; in group II 34.3% cases and group III 40.7% cases were mild to severe PEM.

DISCUSSION

The liver is vulnerable to injury from drugs and many other toxins because of its unique anatomy and physiology. The liver has many functions-secretory, synthetic, metabolic and detoxifying roles. In its metabolic roles, it transforms some drugs into toxins that can cause injury to hepatocytes. In the present work of antitubercular drug induced hepatic dysfunction in children 75 children suffering from different types of TB have been evaluated and analysed during first 3 months of therapy. As described before the patients were grouped accordingly to different drug regimens.

Group I: In this group 16 patients were studied. The patients received 5 mg/kg of INH and /or 20 mg/kg of streptomycin for 2 months, 25 mg/kg of ethambutol for first 2 months and then 15 mg/kg for the rest of the period. Only 3 patients showed asymptomatic hepatic dysfunction (rise of serum transaminase level) during the therapy, making 21.3% of the patient studied in this group. The elevated SGPT ranged from 26-45 units/ml. The interval between starting therapy and rise of transaminase was ranged

from 3rd to 5th week. The transaminase came down to normal within 2-4th weeks despite continuity of the therapy. None of these children developed jaundice or hepatomegaly or both. In patients of group I, we found incidence of hepatotoxicity in 20% of the patients and our study is comparable with study of Mitchell JR. Mitchell JR [9] obtained incidence of hepatotoxicity with INH was 12-20%. The two important metabolites of INH after hydrolysis are isonicotinic acid and monoacetyl hydrazine. Monoacetyl hydrazine can be acetylated either to diacetylhydrazine which is nontoxic or to a hepatotoxic acetylating agent due to hepatic microsomal enzyme induction with concurrent use of rifampicin [10] Due to its high efficacy; isoniazid (INH) remains the drug of choice for treatment of latent tuberculosis (TB) despite the fact that it can cause liver failure [11].

In our study we studied effect of drug only for 10-12 weeks. Our study comprises patient age group 2 months to 12 yrs. Starke JR *et al*. [12] reported hepatotoxicity due to INH occurred in 15% of adult patients. However, in children, incidence was much lower i.e. 3-10% with serious jaundice occurring in only 6% of cases.

Asymptomatic rise of transaminase in 18.75% patients in present study correlates with the finding of Mitchell *et al*. [9] and closes to Mehta *et al*. [13]. The high incidence in our study is explained by high incidence of PEM in children coming to our hospital. Jaundice, hepatomegaly or both or any other signs and symptoms of liver disease was not found during present study group I.

Group II: This group comprised of 32 patients and they received 10mg/kg INH, 15 mg/kg of Rif and 30 mg/Kg of streptomycin or 25 mg/Kg of ethambutol for the first 2 months and then 15 mg/kg for the rest of the therapy period. Out of 32 patients 9 patients showed asymptomatic hepatic dysfunction (raised SGPT) which made up to 28.12% of cases and 2 patients (6.2%) had developed symptomatic hepatic dysfunction. The appearance of jaundice is more when INH and rifampicin was given together as compared to INH alone. In accordance with study of TB Research Centre, Madras; National TB Research Centre, Bangalore, 1986 the incidence of hepatotoxicity in short course regimen and other regimen containing both INH and rifampicin was found to be 24% [14]. Mehta S *et al*. [13] study reports also fall in line to our study as he noted incidence of hepatic dysfunction in 38.3% of the study patient. Rao and Wadia study [15] results showed incidence of hepatic dysfunction only 17.4% patients which does not follow our study results. This variation may be due to genetic variation, individual susceptibility and variation in the sample size. Genetic variations between individuals and population in the acetylation of INH are well known. Smith *et al.* [16] have shown difference in transaminase elevation between slow and fast acetylators.

Group III: In this group 27 patients received 10 mg/kg INH, Rif 15mg/kg and PZA 30mg/kg, and Streptomycin 30 mg/kg or ethambutol 25 mg/kg were added to make it a four drug regimen, which is advocated for the treatment of neurotuberculosis. Eight patients showed asymptomatic hepatic dysfunction (increased SGPT) 29.65 during the course of treatment. Three patients have developed symptomatic hepatic dysfunction (11.11%). The highest level of SGPT was 120 IU/ml. The enzyme came down to near pre-treatment level within 4th week after elevation. Comparing the percentage of patients developing hepatic dysfunction between group II and III, we find slightly higher toxicity with the addition of PZA to INH and Rif and least incidence of hepatic dysfunction found in group I (= 20%).

Nutritional status with relation to hepatic dysfunction due to anti-tuberculous drugs:

In the present study, children with PEM demonstrated a higher incidence of hepatotoxicity, which may be related to their limited capacity to handle the drug. In group I and group III as the degree of malnutrition increases, incidence of hepatotoxicity also increases. In group II incidence of hepatotoxicity more found in mild to moderate PEM as compared to severe PEM. Mehta *et al*. [13] and Buchanan N *et al*. [17] suggested that the drug metabolising process in the liver is deranged in the state of PEM, thus affecting adversely the pharmacokinetics of drugs metabolized in the liver. Acetylation pathways have been shown by Mehta *et al*. [13] be deranged causing a slower rate of metabolism of the sulfadiazine in PEM. INH is also metabolised by the same pathways and so is likely to be affected.

Age with relation to hepatic dysfunction

Hepatotoxicity of the drug in the different age group shows it is more prevalent in the younger age group. We found the highest percentage of toxicity in 2 months to one year of age group and 2nd highest in 3 to 6 yrs of age group. Similar findings had been noted by Mehta and Rugmini [13] as they found maximum number of hepatotoxicity in children below 5 yrs of age. Thulasimany *et al.*[18] had suggested that young age may increase hepatic injury with the hepatotoxic drugs. Immaturity of the metabolising enzyme has been attributed to the hepatotoxicity in younger age. Bistrizer *et al*. found that young age may increase the rapidity of the onset of severity of hepatotoxicity when combination therapy is used [19]. Our findings are consistent with that of Mehta *et al*. [13] and Thulasimany M [18].

When INH hepatotoxicity was recognized it was already known that exposure to INH and its metabolites varied; there were probably three N-acetyltransferase 2

(NAT2) phenotypes, rapid, intermediate and slow acetylators of INH and there was great interest in the NAT2 phenotype in relation to ADIH. With definitive genotyping it is now indisputable that SS acetylators of INH are more likely to experience a rise in serum hepatic transaminases than rapid acetylators [20-23].

Different mechanisms for hepatotoxicity have been studied-cytochrome P450-dependent toxicity, bile-induced hepatocyte apoptosis, and mitochondrial dysfunction and peroxynitrite toxicity. However, it is generally thought that many mechanisms play out in ATT hepatotoxicity [24]. Of utmost importance is the occurrence of ATT hepatotoxicity as it can affect compliance, outcome of management and result in death [25, 26].

CONCLUSION

We studied 75 patients of tuberculosis; groups have been divided into three groups according to drug combination they received. In patients of Group I (16 patients) we used INH along with streptomycin or ethambutol; in patient of Group II (32 patients) we have INH+ Rif along with streptomycin or ethambutol and in patients of Group III (27 patients) we used INH + Rif+ PZA along with streptomycin or ethambutol. In cases of INH only or INH with streptomycin or ethambutol, there was no case of clinical hepatotoxicity in the form of hepatomegaly and jaundice. Clinical hepatotoxicity in the form of hepatomegaly and jaundice was present more in group II cases taking INH+ Rif which was 6.2% and further it increased to 11% when PZA also added. Higher incidence of increase in SGPT was noted in group III with INH with Rif +PZA. Overall hepatotoxicity in our study was 33.33%. Maximum toxicity occurred after only 2 weeks of ATT. There was inverse correlation of toxicity with the age of patient. There was direct correlation of severity of malnutrition to toxicity of ATT in the study cases. As study was small further large scale study will be needed to make guidelines for monitoring and early detection of hepatotoxicity in patients suffering from various types of tuberculosis and taking ATT.

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