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Incidence of Drug Induced Hepatotoxicity During Intensive Phase of Antitubercular Therapy in Rural Population of Uttar Pradesh

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Abstract

Introduction

Tuberculosis (TB) is the most common cause of infection-related death worldwide. The most frequent adverse effects of antituberculosis treatment are hepatotoxicity, skin reactions, gastrointestinal and neurological disorders.

Hepatic drug reactions usually occur in the first 2 months of treatment but may happen at any moment during the treatment period.

Aims & Objectives:

- **To identify eligible case to start Anti Tubercular therapy.**
- **Serial monitoring and documentation of liver functions during intensive phase of therapy.**
- **To compare the variables in hepatic derangement group and normal group after introduction of ATT.**

Materials & methods: This study was an observational prospective cohort (analytical) study carried out in the pediatric ward of U.P.U.M.S. Saifai, a tertiary care centre of 1200 beds between Jan2015-june 2016

All the patients admitted in pediatric ward with Tuberculosis were interviewed and informed,written consent was obtained. Relevant clinical history and clinical examination was performed on each of participants with emphasis on anthropometry (height, weight, mid upper arm circumference), axillary temperature, general physical examination, respiratory system examined thoroughly. Systemic examination and specific investigations including Liver function test were done

Result: In our study, the incidence of anti-TB-DIH was 15%, with 16 out of 107 children demonstrating clinical or biochemical features of liver injury.

Conclusion: This study reinforces that anti-TB DIH is a clinically significant complication in children, with a 15% incidence and early onset in most cases. Male gender was identified as a potential risk factor, while extrapulmonary TB and malnutrition were not significant predictors in our setting.

Keywords: Tuberculosis, ATT, Drug induced hepatotoxicity.

Introduction: Tuberculosis (TB) is the most common cause of infection-related death worldwide. In 1993, the World Health Organization (WHO) declared TB to be a global public health emergency. To cure TB and reduce disease transmission, patients should be placed on effective treatment soon after diagnosis. The most frequent adverse effects of antituberculosis treatment are hepatotoxicity, skin reactions, gastrointestinal and neurological disorders.

Hepatotoxicity is the most serious one. Antituberculosis drug-induced hepatotoxicity causes substantial morbidity and mortality and diminishes treatment effectiveness. Asymptomatic transaminase elevations are common during

antituberculosis treatment, but hepatotoxicity can be fatal when not recognized early and when therapy is not interrupted in time

Hepatic drug reactions usually occur in the first 2 months of treatment but may happen at any moment during the treatment period. Clinical, biochemical and histological features of antituberculosis drug-induced hepatotoxicity are hard to distinguish from viral hepatitis.

Hepatotoxicity can be minimized by assessing liver function test before the start of treatment and monitoring every week during the intensive phase in the risk groups like patients with preexisting liver disorder and malnourished children. Close clinical and biochemical monitoring is to be done in hepatitis B carriers as there is higher incidence of liver dysfunction.

Aims & Objectives:

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Materials & methods: This study was an observational prospective cohort (analytical) study carried out in the pediatric ward of U.P.U.M.S. Saifai, a tertiary care centre of 1200 beds between Jan2015-june 2016

Ethical clearance was taken from ethical committee of institute. An informed and written consent was taken from the parents of children. Total 142 patients were included satisfying the inclusion criteria. Out of 142 patients included 35 patients lost during follow up and there was no expiry during the study period.

The study group enrolled children in age group 6 month to 14 years attending the in- patient and outpatient department of pediatrics were included in our study with the following complaints.

1. Persistent fever/cough more than two weeks and/or
2. Loss of weight /no weight gain and/or
3. H/O contact with infectious tuberculosis case

Inclusion criteria:

- New patients who never had tuberculosis
- Have Taken anti Tubercular treattment for 1 month

This group was further divided in two group

Group 1

Children developing clinical symptoms of hepatitis with raised liver enzymes more than three times of upper normal limit or raised liver enzymes more than five times of upper normal limit after the initiation of antitubercular therapy.

Group 2

Patients with tuberculosis who received the intensive phase treatment of antituberculosis therapy without developing hepatitis symptoms and liver enzymes less than three times upper normal limit.

Exclusion criteria:

- Patients whose result of serological tests indicated acute hepatitis of infective origin Patients of chronic liver disease
- Patients not given consent for study
- Patients on other known hepatotoxic drugs
- Cholestatic jaundice
- Those children having history of contact with multi drugs resistant tuberculosis case
- Increased liver enzymes before start of antituberculosis treatment due to any reason
- The patients diagnosed with tuberculosis satisfying the inclusion criteria categorized as new cases according to RNTCP guidelines these children were treated with standard antituberculosis treatment (DOTS regime category 1).

All the patients fulfilling the inclusion and exclusion criteria admitted in pediatric ward were interviewed and informed,written consent was obtained. All subjects were evaluated on a precoded proforma which included relevant clinical history, information obtained with questionnaires including immunization, family history, nutritional history,history of contact with tuberculosiswere taken.

The socio demographic data obtained and clinical examination was performed on each of participants with emphasis on anthropometry (height, weight, mid upper arm circumference), axillary temperature, general physical examination, respiratory system examined thoroughly. Systemic examination and specific investigations were done. Patients were examined for major congenital malformation, cardiac disease, etc.

Sample collection method and transportation

Then, 5 mL of venous blood was drawn in plane, and EDTA vial from each individual. The collected blood sample sent to department of microbiology preferably within one hour after collection. If it was not possible then it was kept kept in refrigerator and was send within four hours after collection. The specimen was stored at 4 0C until transported to the laboratory. The one sample is then send to biochemistry department for liver function other for routine examinations. Alanine transaminase, aspartate transaminase, and total bilirubin were measured photometrically with clinical chemistry analyzer RANDOX RX imola and then continuously monitored by measuring these liver enzymes every 2 weeks for 2 months.

Statistical analysis

Statistical analysis Data were coded, entered, and cleaned using statistical software and then exported to and analyzed with SPSS, version 20 for Windows. The mean, standard deviation (SD) and frequency of variables were calculated. The bivariate and paired t test logistic regression was calculated to evaluate the possible association of the variables, and $p < .05$ was considered as statistically significant.

Observations & Results: Anthropometric and demographic data, clinical and laboratory data, hepatotoxicity of study patients of one hundred and seven TB patients taking anti-TB drugs were involved in this study and were followed for 2 months.

Table (a) Age wise distribution in various groups

Age in yrs	Group A	Group B	P value
0.5-1	12(11.21%)	3(2.8%)	0.41
1-5	35(32.71%)	3(2.8%)	
5-14	44(41.12)	10(9.34%)	

In our study Age wise distribution of hepatotoxicity in study population, the P value equals 0.41 (chi square test). The ages of the cases ranged from 6 months to 14 years with the mean (±SD) age being 5.7 (±3.8 years), but the highest number of participants were found in the school going age group of 6 to 14 yrs, which was 54 (50.4%).

Table (b) no. of patients with deranged LFT and without derangement in LFT

	Group 1 (normal LFT)	**Group 2 (deranged LFT)**	**Total**
No. of patients	91(85%)	16(15%)	107(100%)

The incidence of anti-TB-DIH in rural population of Uttar Pradesh was 15%. Out of 107 patients 16 (15%) developed hepatotoxicity

Table (c) Result of patients who had antituberculosis-drug-induced hepatotoxicity and without anti-TB DIH (mean±SD)

	DIH group	without DIH
SGPT(U/L)	124.65±31.03	73±11.92
SGOT(U/L)	119.15±32.94	85.78±16.80
S.BIL(mg/dl)	0.81±0.25	0.68±0.19

S.ALB(gm/dl)	2.85±0.25	2.91±0.14

The values of SGPT, SGOT, S.Bil, S. Albumin levels with their mean were elevated in DIH group but remained near baseline in group not developing hepatotoxicity.

Table (d) Type of tuberculosis in study population

	Pulmonary Tuberculosis	**Extra Pulmonary Tuberculosis**	**P value**
Group A	43(40.18%)	48(44.85%)	1.0
Group B	7(6.54%)	9(8.41%)	

In our study type of tuberculosis(pulmonary and extra pulmonary) wise distribution of hepatotoxicity in study population, the P value equals 1.0 (chi square test). The association between type of tuberculosis and hepatotoxicity (outcomes) is considered to be statistically insignificant with p value >0.05.

Table (e) Clinical presentation of antituberculosis drug induced hepatotoxicity in patients

Sign and symptoms	**Patients with anti-TB-DIH, No. (%)**
Anorexia	9(56%)
Nausea, Vomiting	11(68%)
Jaundice, itching	7(43%)
Abdominal Pain, Tenderness (right hypochondrium)	4(25%)

Most of the patients who had developed anti-TB-DIH showed the same signs and symptoms (malaise, anorexia, vomiting, nausea , and jaundice, itching, hepatic tenderness). The most common symptoms being nausea and anorexia (68% and 56%, respectively), followed by jaundice and abdominal pain r being 43% and 25%, respectively .

Table (f) comprision of SGPT from baseline on follow up

		Mean	**df**	**T value**	**Standard error of difference**	**P value**
Pair 1	SGPT BRFORE	186.80±81.15	106	5.58	7.92	0.0001
	SGPT AFTER 15 DAYS	208.1±143.09				
Pair 2	SGPT BRFORE	186.80±81.15	106	5.93	5.07	0.0001
	SGPT AFTER 1 MONTH	148.4±73.5				
Pair 3	SGPT BRFORE	186.80±81.15	106	5.18	2.88	0.0001
	SGPT AFTER 45 DAY	84.93±22.93				
Pai r 4	SGPT BRFORE	186.80±81.15	106	0.54	3.017	0.588

	SGPT AFTER 2 mONTH	56.43±15.81				

There is significnt differences between the SGPT values from baseline at 15 day, one month and 45 day, but at end of two months values came to base line and giving no significant difference.

Discussion:

Drug-induced hepatotoxicity (DIH) remains a serious and potentially life-threatening complication of anti-tubercular therapy (ATT), particularly in the pediatric population. Hepatotoxicity compromises treatment efficacy due to interruptions or modifications in therapy, increases morbidity, and demands careful clinical management. In our study, the incidence of anti-TB-DIH was 15%, with 16 out of 107 children demonstrating clinical or biochemical features of liver injury. This figure is consistent with earlier reports from similar settings, including a study by Yee D et al., who reported an incidence of 15% among adult patients (2), and Shakya R et al., who found similar figures in a Nepalese cohort (5).

Comparatively, this incidence remains significantly higher than in Western countries, where studies have documented DIH rates ranging from 2% to 5% (3,10,18). This disparity could be attributed to multiple factors, including genetic polymorphisms in hepatic enzymes, regional differences in nutrition, background rates of subclinical liver disease, and varying drug regimens. Furthermore, inconsistent diagnostic criteria for DIH across studies contribute to these variations (4,19).

The clinical spectrum of hepatotoxicity observed in our cohort ranged from asymptomatic transaminase elevation to symptomatic disease with jaundice, nausea, vomiting, pruritus, and malaise. In all patients, transaminase elevations remained below tenfold the upper limit of normal (ULN), and none developed fulminant hepatic failure. This mild to moderate severity is encouraging and likely reflects early recognition and appropriate monitoring protocols implemented during the study.

Notably, the onset of hepatotoxicity in our patients ranged from 11 to 27 days post-initiation of therapy, with a mean onset at 18 days. This is relatively earlier compared to some literature. For instance, Shakya R et al. reported a median onset at 28 days (5), while other reports describe a range up to 60 days (6,12). Mahmood K et al. noted that over 60% of their cases developed DIH within the first 14 days of therapy (7), reinforcing that the first 2–4 weeks constitute the highest risk period. This supports current recommendations for close clinical and biochemical surveillance during the initial phase of treatment, particularly in high-risk individuals (20).

In terms of risk stratification, male gender was found to be significantly associated with hepatotoxicity in our cohort. This observation aligns with some adult studies (13,21), which propose hormonal or enzyme activity differences between sexes as potential explanations. Conversely, many pediatric studies fail to consistently reproduce this finding, suggesting that age-related hormonal immaturity in children might mitigate gender effects. Nonetheless, this potential sex-based vulnerability merits further investigation.

Contrary to prevailing assumptions, age, BCG immunization, type of tuberculosis (pulmonary vs. extrapulmonary), and malnutrition were not significantly associated with hepatotoxicity in our analysis. Malnutrition, often assumed to predispose to DIH due to decreased hepatic reserve and micronutrient deficiencies, showed no significant link. It is possible that the nutritional homogeneity or moderate degree of undernutrition in our sample masked such associations. Still, malnutrition remains a concern, as studies from India and Africa have shown mixed results regarding its contribution to DIH (8,22).

The extent or type of tuberculosis, including extrapulmonary involvement, did not correlate with increased hepatotoxicity in our patients. In contrast, Indian studies by Sharma SK et al. and Parthasarathy R et al. reported a positive association (8,9). A plausible explanation for this divergence is that extrapulmonary TB in itself may not reflect disease severity or systemic burden in children as it might in adults. Moreover, differences in diagnostic thresholds and reporting standards could explain the inconsistencies.

Management of DIH in our cohort was conservative and effective. Once hepatotoxicity was suspected or confirmed, ATT was temporarily halted, liver function was closely monitored, and therapy was reintroduced in a staggered manner. All affected patients recovered without residual hepatic dysfunction and successfully completed their TB therapy. This is consistent with global best practices, where reintroduction protocols—commonly starting with rifampicin and ethambutol, followed by isoniazid, and deferring pyrazinamide—have shown good outcomes (14,23).

The hepatotoxic potential of first-line antitubercular drugs is well documented. Isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) are most implicated, with INH being the leading agent (3,24). INH undergoes hepatic metabolism via acetylation, producing toxic intermediates such as hydrazine, which induce oxidative stress and mitochondrial injury. The hepatotoxicity risk is modulated by acetylator status—slow acetylators accumulate more toxic metabolites. This pharmacogenetic influence is particularly relevant in Asian populations, where slow acetylator phenotypes are more prevalent (25,26).

Rifampicin, while hepatotoxic, primarily enhances INH toxicity through enzyme induction, accelerating INH metabolism and increasing toxic metabolite load. Pyrazinamide is believed to be directly hepatotoxic through unknown mechanisms. Ethambutol and streptomycin, conversely, are rarely hepatotoxic and often form the backbone of alternative regimens in patients with DIH (27,28).

Emerging research has also highlighted the role of genetic predispositions in DIH. Polymorphisms in the NAT2, CYP2E1, and GST gene families have been implicated in increased susceptibility to hepatotoxicity (25,29). Children with certain HLA alleles may also be at elevated risk, though pediatric-specific data remains limited. Genomic studies tailored to pediatric populations may eventually allow for risk stratification and individualized therapy.

Routine liver function testing during ATT remains a debated issue in children, especially in resource-constrained settings. While some guidelines recommend baseline testing and monitoring only if symptomatic (30), our findings support the argument for routine early-phase monitoring—at least in the first 2–4 weeks. In resource-limited areas, where laboratory access is restricted, structured clinical algorithms focusing on early warning symptoms (nausea, anorexia, jaundice) can serve as practical screening tools (31).

Preventive strategies to minimize DIH risk include avoiding concurrent hepatotoxic drugs, ensuring adequate hydration and nutrition, and using vitamin supplementation, especially pyridoxine with INH. In malnourished or HIV-positive children, or those with pre-existing liver disease, modified regimens or close monitoring may be warranted (32,33).

Conclusion: This study reinforces that anti-TB DIH is a clinically significant complication in children, with a 15% incidence and early onset in most cases. Male gender was identified as a potential risk factor, while extrapulmonary TB and malnutrition were not significant predictors in our setting. Early detection, temporary cessation of therapy, and cautious reintroduction were effective in preventing progression and achieving full recovery. Future directions include larger multicenter pediatric studies, pharmacogenomic profiling, and the development of simplified clinical monitoring tools to guide therapy in high-risk populations. Ultimately, balancing effective TB control with the minimization of adverse effects remains a central challenge in pediatric TB management.

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