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Original Research Article

A study of adverse drug reactions in tuberculosis patients in a tertiary care hospital

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ABSTRACT

Background: Tuberculosis is the most rambling communicable infectious disease on earth. It is the single most common cause of death in individuals aged 15-49 years. Adverse drug reactions to antitubercular drugs causing significant morbidity, mortality, incurring substantial additional costs because of added outpatient visits, tests, and hospitalizations. Study was carried out with objectives of assessing the rate and type of adverse drug reactions (ADRs) and detecting serious and preventable ADRs with collection of demographic details of patients taking antitubercular drugs and developing ADRS.
Methods: A cross sectional, prospective, observational study conducted in department of chest and TB of a tertiary Health care and teaching hospital in both IPD and OPD patients for a period of 18 months. 480 patients monitored.
Results: Among 480 patients 120 i.e., 25% developed ADR. frequency being significantly higher in males (58%) and adult age group (>18 years) amongst hospitalized comparing to outdoor patients the gastrointestinal tract [GIT] (39%) followed by, generalized body disorders (19%) hepatobiliary system (17%) were organ systems most affected Majority (56%) ADRs reported in 0-2 month of starting therapy (63%) of cases were in "probable according to Naranjo causality assessment (37%) being possible. 55% ADRs were moderate in severity followed by 36% mild and 9% severe. 30% of ADRs were definitely preventable followed by 20% of probably prevented according to schumock thronstone preventability scale
Conclusions: Study highlights the importance of routine monitoring and robust pharmacovigilance system for success of national tuberculosis programmes in India as well as worldwide.

Keywords: Adverse drug reactions, Tuberculosis, Pharmacovigilance

INTRODUCTION

Tuberculosis an infectious disease caused by Mycobacterium tuberculosis, It is the most rambling communicable infectious disease on earth and remains out of control in many developing countries. It is the single most common cause of death in individuals aged 15-49 years.[1,2] India features among the 22 high TB burden countries and has accounted for an estimated one quarter (26%) of all TB cases worldwide.[3] Pulmonary tuberculosis is the most common presentation. Good bacteriological diagnosis and compliance on treatment are the two core stakes of successful treatment of pulmonary tuberculosis. In order to strengthen the efforts to control TB, Government of India introduced the revised national tuberculosis control program (RNTCP) in 1993, that implemented DOTS.[4,5] One of the key component of DOTS therapy is the standard anti TB short course chemotherapy regimen, which requires continually taking drug combinations for 6-9 months.[6] Despite all these initiatives and positive therapeutic effects, studies have shown that utilization of multidrug regimens can

cause undesirable adverse drug reactions (ADRs) of varying degrees of severity.[7] Such as hepatotoxicity, gastrointestinal (GI) disorders etc.

It has achieved global benchmark of treatment success consecutively for the last five years as the prevalence of ADRs observed in various studies conducted worldwide ranged from 8% to 85% and prevalence of 2.3% to 35% in various Indian studies.[8-12] Adherence to the long course of TB treatment is intricate, dynamic phenomenon with a varied range of factors impacting on treatment taking behaviour. Treatment interruption among tuberculosis (TB) patients and its implications are well known. One of the main reasons for treatment interruption among TB patients is adverse drug reactions (ADRs). Adherence to anti-tubercular treatment is also a major challenge faced by both the policy creators and health authorities. According to WHO "an adverse reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of a disease or for modification of physiological function".[13] It is likely that many of them particularly the avoidable and potentially avoidable ones may be minimized by patient and physician education and better prescribing practices and thus lead to considerable cost savings.[2] Considering adverse reactions to antituberculosis drugs may be related to various factors such as the dose and time of day at which the medication is administered, patient age, nutritional status, the presence of pre-existing diseases or dysfunctions like impaired liver/kidney function, alcoholic etc. National TB programs are generally well structured to monitor patients using standardized indicators, but currently no system of pharmacovigilance to collect information on ADRs directly, treatment interruption and loss to follow-up (LTFU). Once a patient is LTFU, the chances of favourable treatment decline, and the problem multiplies if drug resistance develops.[14] There is a dearth of published literature about anti-TB drug-induced mortality morbidity and reduced quality of life, particularly in low-resource settings. Data regarding ADRs related to anti tubercular therapy are scant in local population.[15] Drug safety has been included in curriculum guidelines for Indian medical undergraduates (MCI Curriculum Guidelines, 1997) but little has been achieved in this regard.[17] Monitoring of adverse drug reactions should be a collaborative activity of both clinicians and pharmacologists. At present, in India, the pharmacologists usually do it with or without the involvement of clinicians.[2] Physicians, however, continue to play a meaningful role in the entire monitoring process, as the co-operation of clinicians is needed to have access to patient data and interpretation of the reports of suspected adverse drug reactions "Pharmacovigilance needs to be an integral accompaniment to treatment programs as they expand their geographical coverage, given that the frequency and expression of ADRs may be influenced by factors linked to the demographic, genetic and nutritional patterns, and to the background comorbidity in a population.[2]

METHODS

This was a cross sectional, prospective, observational study of adverse drug reactions in the tuberculosis patients that was conducted in department of chest and TB of a tertiary health care and teaching hospital in both IPD and OPD patients Data was collected for over a period of 18 months from December 2016 to July 2018.

Sample size was calculated by Open Epi software with (95% CI) using formula

$$Sample\ Size\ = 4PQ/L$$

Where P=Prevalence, Q=(100-P), L=(Error Percentage), wherein the prevalence of ADRs due to TB according to previous studies was 2.5% to 33%.[8] Approval from institutional ethics committee and HOD Of Chest and TB was taken prior to commencement of the study. Study were conducted maintaining strict confidentiality of prescribing physician and the patient. Information regarding age, weight, sex, symptoms, category, co-morbid conditions, HIV status, date of initiation, completion and duration of treatment of therapy, history of previous Anti-TB therapy any problem with the therapy, other medications. Followed for period of as long as admission to IPD patients and as long as they were on treatment, during their routine outdoor visiting schedule for outdoor patients or 18 months. Patients with ADRs visiting OPD as well as that occurred during hospitalization and ADRs that led to hospitalization details were recorded monitored and without interfering management of patient. Detection and monitoring was done by interviewing patients, reviewing laboratory tests and medical charts. Consulting with physicians about the patients clinical problems. Information regarding ADR were recorded as per the C.R.F (case record form).

Inclusion criteria

Inclusion criteria for current study were; total 480 IPD and OPD patients of any age and both sex, who were diagnosed with Pulmonary Tuberculosis belonging to CATI and CATII (RNTCP guidelines 2010) with or without other respiratory co-morbidities taking drugs of category as per DOTS and willing to be part of study were included.

Exclusion criteria

Exclusion criteria for current study were; patients with non-pulmonary form of tuberculosis, chronic hepatic illnesses such as cirrhosis, chronic hepatitis and acute viral hepatitis, patients with TB and HIV on HAART and not willing to and unable to sign consent form.

Analysis of data

Hepatitis defined as increased liver enzymes more than five times the base line accompanied with clinical

symptoms including jaundice, nausea, vomiting, abdominal pain and anorexia. Hyperuricemia defined as a serum uric acid (SUA) level greater than 8.0 mg/dl, the approximate level at which urate is supersaturated in plasma. The Naranjo's algorithm: scale used to assess causality or temporal relation between adverse event and drug therapy. ADR is assigned to a probability category from the total score as follows Score of 9 or greater definite ADR, score of 5-8=probable ADR, Score of 1-4=possible ADR, Score of 0=doubtful if the ADR. Modified Hartwig and Siegel's Scale: This scale used to find the severity of ADR, Levels decided by the answering to relevant level of question and categorized as Mild=level 1and level 2, moderate=level 3 and level 4, severe=level 5, level 6, level 7. Shumock and Thornton Scale: (preventability) preventability of ADR categorized as definitely preventable, probably preventable and not preventable. Any answer of "yes" to any question was suggesting ADR as preventable of that category (definitely/probably) and none of answer were yes that ADR were classified as not preventable. ADRs were recorded in standard CDSCO suspected adverse drug reaction form.

Data analysis

Data analysis was performed using Microsoft Excel 2013 results were expressed as numbers and percentages. $p<0.05$ was considered as statistically significant.

RESULTS

Demography

Among 480 patients that were observed during study period 120 patients developed total 122 adverse drug reactions.

Table 1: Distribution of patients according to demography.

Demography	Patients with ADRS (N=120) Frequency (%)	Patients without ADRS (N=360) Frequency (%)	Total (n=480) Frequency (%)	Range and mean	P value
Male	70 (58)	250 (70)	320 (67)		**0.025
Female	50 (42)	110 (30)	160 (33)		
<18 yrs	15 (12)	40 (11)	55 (22)	7-70 years	0.68
>18 yrs	105 (88)	320 (89)	425 (88)	39.5±15	
<50 kg	92 (77)	280 (78)	372 (78)	13-78 kg	0.802
>50 kg	28 (23)	80 (22)	108 (22)	40.25±14.5	
CATI	95 (79)	265 (73)	360 (75)		0.57
CATII	25 (21)	95 (27)	120 (25)		
IPD	84 (70)	170 (47)	254 (53)		**<0.0001
OPD	36 (30)	190 (53)	226 (47)		
Total	120 (25)	360 (75)			

Z test, **p-value<0.05 is significant

Demographic data analysis reveals that amongst the 480 patients- 120 (25%) developed ADRs during study. Amongst the 120 patients; 70 (58%) were males and rest were females. Only 15 (12%) belonged to paediatric (<18 years) age group and majority 41% to age 41-60 years. 92 patients (77%) belonged to <50 kg weight Category A higher proportion i.e., 95 (79%) of patients were taking CAT-I regime. Indoor patients reported more ADR i.e., 84 (70%) as compared to outdoor i.e., 36 (30%) (Table 1).

Evaluations (assessments) of ADRs

Gastrointestinal system (39%) related ADRs were most commonly reported, followed by generalized body reactions (19%) (Fever, weakness, loss of weight, headache etc.) And liver and biliary system contributes (17%) of ADR reporting (Figure 1). A total 56% ADRs like, nausea vomiting (7), rash (6) generalized body disorders occurred within 2 month of starting therapy (Table 2-3). ADRs like hepatitis (13), weight loss (5), peripheral neuropathy (3) was observed during 2-6 month of therapy initiation and after 6 months, ADRs like peripheral neuropathy visual and auditory impairment were observed (Table 3).

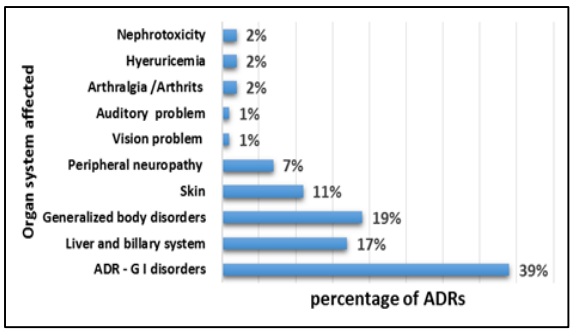

Figure 1: Pattern of ADRs depending on organ system affected.

Causality assessment by Naranjo's causality assessment questionnaire. Majority of ADRs 77 (63%) were from probable category and second 45 (37%) was from possible category (Figure 2). As lack of placebo testing, re challenge and therapeutic drug monitoring or contribution of other reason for ADRs none of ADR were definite category.

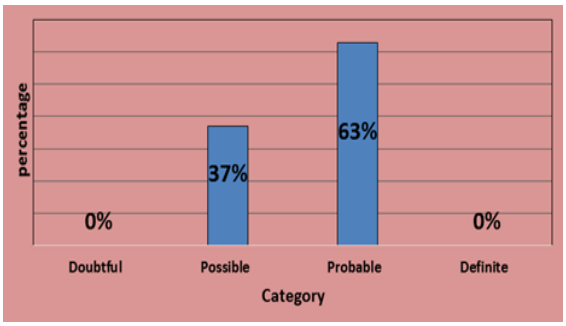

Figure 2: Frequency of ADRs by Naranjo's causality assessment scale.

Table 2: Onset of adverse drug reactions.

Time of onset	0-2 months		2-6 months	>6 months
	<2 week	>2 week		
(N) % of ADRS	(22) 18	(43) 38	(47) 36	(10) 8
	56		36	8

Table 3: Major 3 ADRS according to onset of time.

0-2 month		2-6 month		>6 month	
Headache	2	Hepatitis	13	Peripheral neuropathy	3
Rash	6	Peripheral neuropathy	3	Blurred vision	1
Nausea and vomiting	7	Weight loss	5	Auditory problem	1

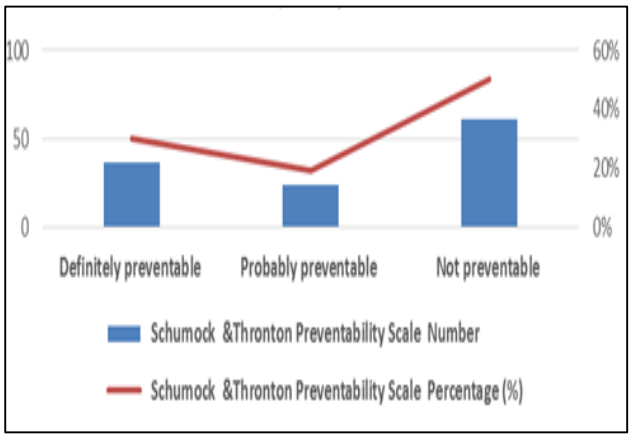

Figure 3: Frequency of ADRs based on preventability by Schumock and Thornton scale.

Maximum ADRs in gastro intestinal system contributes in probable group Nausea andvomiting (29%) second to that were hepatitis (18%), Rash (10%) were most frequent ADRs in probable group. Anorexia (13%) nausea and vomiting (11%) and other generalized body disorders like headache, hypotension anemia were most frequent ADR in possible category (Table 4).

Table 4: Frequency of ADRs (major 3) Naranjo's causality assessment.

Probable group		Possible group	
ADR	**Incidence (%)**	**ADR**	**Incidence (%)**
Nausea and vomiting	29	**Weakness**	7
Hepatitis	18	**Hypotension**	9
Rash	10	**Nausea and vomiting**	11
Others	42	**Others**	73

Table 5: Frequency of ADRs based on modified Hartwig severity scale (n=122).

Level	N (%)	Total	Severity (%)
Level-1	42 (34)	36	Mild (36)
Level-2	2 (2)		
Level-3	42 (34)	55	Moderate (55)
Level-4	25 (21)		
Level-5	10 (8)	9	Severe (9)
Level-6	1 (1)		
Level-7	0 (0)		

55% of ADRs belong to moderate category (level 3 and level 4), 36% ADRs falls in mild category (level1 and level 2) which doesn't require to any special treatment or antidote or to change current regime but some patients by withhold it (Level-2) for duration without other changes. whereas severe group entail 9% ADRs (Table 5). Out of 122 majority 62 (50%) ADRS were not preventable. Followed by 36 (30%) definitely preventable and only 24 (20%) were Probably preventable (Figure 3). During the study period of the 122 ADR 43 (35%) recovered, whereas majority of patients 61 (50%), recovering (Figure 4).

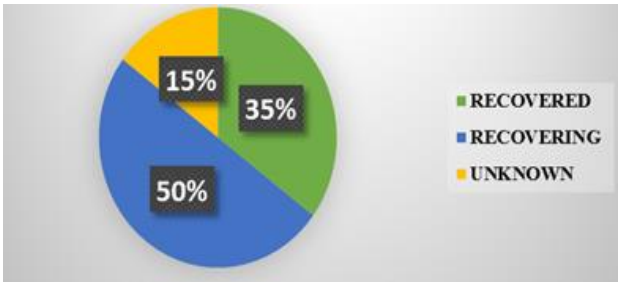

Figure 4: Outcome of ADRS.

DISCUSSION

The incidence of adverse drug reactions among Pulmonary Tuberculosis patients in our hospital during the study period was found to be 25% which is in accordance with earlier studies who reported comparable incidence of 18.20% to 25.01%.[17-19] Whereas in some studies showed higher incidence of ADRs 48%-80%.[20,21] This divergence can be ascribed to disparities in the study settings and differences in the geographical and physical factors of the sample population. Out of 120 patients statistically significant number of ADRs were observed in males (58%) in consonance with other Indian studies.[19,22] due to higher enrolment. Only 12% belonged to paediatric age group i.e.,18 years due to hurdles in diagnosis and reporting of ADRs in children. Highest reporting in age group 40-60years was in concordance with other Indian studies.[17] Majority patients having ADRs were <50kg accordance with Indian study.[23,24] About 79% ADR were reported amongst patients taking CATI regime which is in accordance with other study.[23] 70% of the ADR cases were reported from IPD because of hospitalized participants were likely to have more complex and serious diseases and were monitored more frequently, thus increasing the chances of discovering ADRs.[25] Majority of ADRs were related to GIT (39%) followed by generalized body disorders (19%), liver and biliary system (17%), and others.

The increased incidence of GI side effects could be attributed to multiple drug therapy as a major predisposing factor for ADRs. Higher rate ADRs occurrence with intensive phase treatment which matches with other study.[26] Certain ADRs like hepatitis, hyperuricemia, nephrotoxicity neurotoxicity not recognizable easily by patients and require investigations hence reported in intermediate period (2-6 months). This observation rings a bell that there is a need of rigorous monitoring for early detection subsequent prevention of such ADRs that are probably associated to anti-tubercular treatment which were seen to be reported late period >2/6 months. Majority of the reactions were found to be moderate as a proper treatment measure was required even after the suspected drug was held discontinued or changed i.e., antacids, NSAIDS, antibiotics etc.[27] Contradicting the finding of present study observed higher reporting 73% of mild ADRs due to vigilant reporting. Contradictory to reports in literature present shows 50% ADRs were non preventable but brighter side was 30% these reactions were definitely preventable.[25,27] Noting a detailed history of reaction or known allergy may help reduce them. In the 33 cases of ADRS (27%) continues current treatment without any change or any symptomatic treatment similar to study.[28]

Strengths and limitations

Study provides an insight to the need of implementation of robust pharmacovigilance program and appropriate patient counselling that emphasize on follow up visit, which will help in early identification of ADRs that occur within 2 weeks of initiation of treatment. Limitation of current study was association of ADR with risk factors like alcohol, smoking, etc. could not be established due to missing data.

CONCLUSION

The present study highlights differences in ADR reporting based on parameters like sex and age. More number of males had been enrolled and had reported as compared to the female counterparts ADRs. Similar findings were observed in age group 40-60 yrs. who had a higher ADR reporting as compared to paediatric age group. These observations thereby stress on the importance of detecting and identifying TB in the said groups. The most common ADRs were that related to gastrointestinal system but ranged from moderate to severe and therefore need symptomatic treatment. Unlike few ADRs that were of the severe category (e.g., peripheral neuropathy, auditory impairment) but were also probably related to the drug; were reported late after therapy initiation. This indicates that appropriate physician education and early detection or monitoring can play a role in preventing such consequences.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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