Original Article

A Study of Adverse Drug Reaction to First Line Antitubercular Drugs in DOTS

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Tuberculosis (TB) is an infectious disease caused by *Mycobacterium Tuberculosis*. India has adopted and enforced Directly Observed Treatment Short Course (DOTS) strategy to combat TB. The first line medicines in DOTS are more effective and less toxic but still it cause adverse effects like gastritis, hepatotoxicity and skin allergies. This study is proposed to determine the occurrence of such adverse effects in patients under DOTS therapy and to assess their impact if any on patient compliance.

Objectives : (1) To study the demographic and clinical profile of patients diagnosed with TB. (2) To study the Type & Severity of Adverse Drug Reaction (ADR).

It was Prospective observational study done in duration of March 2018 to December 2018, in Patients who had tuberculosis on 1st line Anti Tubercular Treatment on the directly observed treatment short course (DOTS) enrolled and monitored for Adverse Drug Reactions (ADRs). All the ADRs spontaneously reported or identified (by observation and record of patients) by the researcher were recorded and analyzed.

Out of Total 796 patients were enrolled, 102 patients had ADR. There were 61(59.8%) male and 41(40.19%) female. In my study prevalence rate of ADR was 14.96%. Most common manifestation was gastro-intestinal upset (42.15%), followed by hepatitis (28.43%), joint pain (15.68%), Itching and rashes (5.88%), Giddiness and tinnitus (4.9%), visual blurring (0.98%), and Thrombocytopenia (0.98%).

[*J Indian Med Assoc* 2020; **118(2):** 16-9]

Key words **: Tuberculosis, Anti Tuberculosis Drug, Adverse Drug Reaction.**

Tuberculosis is the primary worldwide cause of death due to infectious disease. The WHO TB statistics for India for 2016 give an estimated incidence figure of 2.79 million case of tuberculosis for India[1].

Directly observed treatment, short course (DOTS) chemotherapy is a part of Revised National Tuberculosis Control Programme (RNTCP)[2] which cause Adverse Drug Reactions (ADR) that result in diminished quality of life, increased physician visits, hospitalizations, and even death[3]. Various factors such as the dose and time of day at which the medication is administered, patient age, nutritional status, the presence of preexisting diseases or dysfunctions like impaired liver function, impaired kidney function, HIV co-infection, and alcoholism may be related to adverse reactions to Anti-tuberculosis drugs. The aim of this study is to know the prevalence of ADRs in patients receiving first line Anti-Tuberculosis Treatment (ATT) and to determine the pattern of various ADRs associated with use of anti-tubercular drugs.

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Editor's Comment :

- **It must be kept in mind that severe side effects with anti-TB drugs are common among patients of pulmonary tuberculosis.**
- **They should be followed up by closer monitoring for the side effects related to anti-TB drugs for better management.**

Materials and Methods

This is a prospective observational study conducted at the Department of Respiratory Medicine in LG Hospital, Ahmedabad, Gujarat, from March 2018 to December 2018. All patients those who have TB (PTB+EPTB) and put on treatment under RNTCP (category 1 or category 2) and met inclusion and exclusion criteria were identified. The study was approved by the IRB committee and written informed consent from study group was taken before enrollment.

Inclusion Criteria :

(1) Patients > 15 years.

(2) Having Pulmonary Tuberculosis (PTB) and Extra Pulmonary Tuberculosis (EPTB).

(3) Taking treatment under DOTS in category 1 or 2 of RNTCP regimens in our hospital.

(4) Who gave consent.

Exclusion Criteria :

(1) MDR case and XDR cases.

(2) Previously existing severe cardiac, renal, hepatic disease.

(3) History of recurrent psychotic disorders, alcohol or drug abuse within the previous year.

(4) Pregnant and lactating women.

All registered patients who were taking treatment of tuberculosis according to category 1 or category 2 under RNTCP were observed. Patient who were having ADRs, their relevant findings were recorded during each clinical visit and their responses were documented. Patients were asked to come for follow up every fortnight & in between whenever needed.

Baseline investigations like Complete Blood Count, Liver Function Tests, Renal Function Tests, Serum Uric Acid were done for each patient before starting anti-tuberculous treatment. Relevant investigations according to patients sign and symptoms were repeated if patients developed ADRs.

Severity of the ADRs were classified according to Hartwig *et al*[4] as:

(1) Mild ADR which were self-limiting and able to resolve over time without treatment and did not contribute to prolongation of length of stay.

(2) Moderate ADRs were defined as those that required therapeutic intervention and hospitalization prolonged by 1 day but resolved in <24 hour or change in drug therapy or specific treatment to prevent further outcome.

(3) Severe ADRs were those that were life threatening, producing disability and those that prolonged hospital stay or led to hospitalization, required intensive medical care, or led to the death of the patient.

All the data of patient having ADRs were recorded according to case record form and analyzed. All adverse events, even if it feels minor for the patients were also recorded. Episodes of hepatitis were considered drug induced if transaminases were normal before therapy, increased during therapy, and returned to normal after discontinuation of the responsible drug. Patients with Moderate degree ADR in whom we had to stop anti-tubercular drug, rechallenge was done after patients improved by starting that drug in regimen. Patients were told to return at any time if new or same symptoms or complaints arise during therapy.

Statistical Methods :

Proportions were expressed as percentages and for continuous variables ranges were used with mean and standard deviations. Accordingly Chi-square test was used to compare data.

Result

Adverse drug reactions due to ATT are expected to be present in majority of patient as part of adverse drug reaction. Total 796 patients were enrolled in my study, out of them 102 patient had ADR. There were 61 male and 41 female, % of ADR in Male & Female is 59.8% and 40.19% respectively. In my study prevalence rate of ADR was 14.96%.The age of the patients screened in the study ranges from more than 15 to 75 years. Maximum number of patients were in their 2nd and 3rd decade of life. Statistically significant higher occurrence of ADRs was found in age group of 21-30 years with mean age 23.03±6.7 year ($p<0.001$). In Present study patient with Low BMI were more prone to develop ADR, statistically higher significant ratio in patient having BMI <18.5(36.27%). Out of 102 patients 65(63.72%) having PTB and rest 37(36.27%) were EPTB. Statistically higher significant ratio for developing ADR in patient of sputum positive PTB (58.2%) (Table 1).

Table 1 — *Demographic and baseline parameters of patients having TB and its association with occurrence of ADRs (n=102)*

Parameter	No of patient with ADR (%)	No of patients without ADR (%)	P value
Age (years)			<0.01
≤20	22 (21.56%)	88 (12.68%)	
21-30	28 (27.45%)	97 (13.97%)	
31-40	21 (20.58%)	242 (34.87%)	
41-50	12 (11.76%)	135 (19.45%)	
51-60	11 (10.78%)	102 (14.69%)	
≥61	8 (7.84%)	30 (4.32%)	
BMI (kg/m^2)			<0.01
<18.5	37 (36.27%)	236 (34%)	
18.5-24.9	34 (33.33%)	278 (40.05%)	
25.-29.9	26 (25.49%)	135 (15.12%)	
>30	5 (4.9%)	45 (44.11%)	
Gender			>0.05
Female	41 (40.19%)	274 (39.48%)	
Male	61 (59.08%)	420 (60.51%)	
Site of TB			>0.05
Pulmonary	65 (63.72%)	432 (62.24%)	
Extrapulmonary	37 (36.27%)	262 (37.75%)	
Category			>0.05
Cat – 1	63 (61.76%)	364 (52.44%)	
Cat – 2	39 (38.23%)	330 (47.55%)	
Sputum Status			<0.01
Positive	60 (58.82%)	256 (36.88%)	
Negative	5 (4.9%)	176 (25.36%)	

Different manifestations of ADRs are shown in Table 2. Out of 102 patients, gastro-intestinal upset was the main complaint in majority (n=43) patients due to Rifampicin in mean of 10.34±7.4 days, followed by hepatitis (n=29) due to Rifampicin, Pyrazinamide and Isoniazid in a mean of 28.13±6.01days, followed by joint pain (n=16) due to Pyrazinamide in a mean of 15.2±6.24 days (Table 3).

Table 2 — *Distribution of adverse drug reactions due to directly observed treatment strategy therapy in tuberculosis patients*

System	Manifestations	Patients	Action for ADRs
Gastrobilliary	Nausea, vomiting, epigastric pain	43(42.15%)	Symptomatic treatment
Hepatobilliary	Jaundice	29(28.43)	Rifampicin, Pyrazinamide, Isoniazid stopped temporarily
skeletal	Joint pain	16(15.68%)	Symptomatic treatment, Pyrazinamide stopped temporarily
Otovestibular	Giddiness, tinnitus	5(4.9%)	Streptomycin stopped
Ophthalmologic	Visual blurring	1(0.98%)	Ethambutol stopped
Dermatologic	Itching, rashes	6(5.88%)	Symptomatic treatment
Blood	Thrombocytopenia	1(0.98%)	Rifampicin stopped
Dress syndrome	Fever, cutaneous eruption, thrombocytopenia	1(0.98%)	Rifampicin, Pyrazinamide, Isoniazid, Ethambutol stopped temporarily

Severity assessment :
- 49(48.03%) of the cases were mild (level-1)
- 34(33.33%) were moderate (level 2)
- 19(18.62%) were severe (level 3)
- 0% was lethal (level 4)

Out of the n=102 patients who developed adverse drug reactions, only n= 7(6.86%) patients required complete stoppage of that offending drug, while n=38(37.25%) patients require interruption of treatment and most of the patients n=64(62.74%) were managed with supportive medication without removing anti tubercular drug from their treatment regimen.

Outcome of patients having adverse drug effects are shown in Table 3. Out of these 102 patients, majority n=78(76.87%) declared cured at the end of treatment, while only n=05(4.90%) patients were declared as failure on treatment. In this study n=03(2.94%) patients defaulted during treatment because of adverse drug reaction or because of poor compliance towards anti-tubercular treatment, while n=0 patients had died during the treatment.

Table 3 — *Outcome of anti-tubercular treatment*

Outcome	No of ADR (n=102)	%
Cured	78	76.40
Relapsed	15	14.70
Failure	5	4.90
Default	3	2.94
Alteration in Therapy	1	0.98

Discussion

After implementation of Revised National Tuberculosis Control Programme (RNTCP)[4] the cure of tuberculosis has been possible. One of the common reasons responsible for noncompliance to RNTCP guidelines are development of ADRs.

Among 102 reported adverse drug reactions, the highest numbers of ADRs were observed in males (60.51%) and (39.48%) was observed in female in the ratio of 6:4. A study conducted by Sainul Abideen P et al reveals[5] that the presence of ADR due to TB is more in males than in the females in the ratio of 7:3. Also the National Tuberculosis Program (NTP) and other study summarized as the ratio of occurrence of ADR of TB between male & female were 5:2[6-8].

ADR due to TB was more prevalent in the age group 21-30 years (13.97%) in current study, Edoh and Adjei *et al*[9] found higher incidence of ADR in the age group of 21-40 years. This may be because the people in this age group are usually involved in activities like smoking, large alcohol intake, etc., which results in the weakening of immunity.

In our study, common ADRs were related to GIT system that is gastritis. This can be attributed to multi drug therapy by oral route. The drugs responsible for these side effects were Pyrazinamide and Rifampicin. 29 (28.43%) patients developed hepatic dysfunction as ADRs. The drugs responsible for this side effect were Pyrazinamide, Rifampicin, and Isoniazid. Six patients (5.88%) experienced allergic skin manifestations as ADRs. The drugs responsible for this side effect were Pyrazinamide, Rifampicin, and Isoniazid. 16 (15.68%) patients experienced joint pain, drug responsible for that was Pyrazinamide, 1 patient experienced visual blurring due to Ethambutol, 1 patient had thrombocytopenia due to Rifampicin. Study done by Yee D *et al*[8] showed that rash present in 12 patients, hepatitis in 12 patients, gastric upset in 11 patients and arthralgia in 1 patients. Other study done by Scharberg T *et al*[10] showed hepatotoxicity (11%), exanthema (6%) and arthralgia (2%), study done by Amit Dedun *et al*[11] showed

16 patients had gastritis, 14 patients had skin rash, 7 patients had giddiness, and 1 patient had thrombocytopenia. Most of the ADRs (48.05%) were mild, only 18.62% were severe reaction (hepatic dysfunction). Study done by Yee D *et al*[8] showed 37 patients had severe reaction. Study by Amit Dedun *et al*[11] showed that 30 patients had severe reaction.

According to my study Indian patients experienced Gastrointestinal symptoms more than other symptoms compared to western study, patients who had Rash and Hepatitis due to ATT[8]. Major limitation of the study is that it was a single centre study on few patients. Larger studies directed towards specific population are required before generalizing findings of this study to whole community.

Conclusion

Management of active tuberculosis includes the initiation and the completion of anti-TB therapy, but there may be interruption of treatment due to side effects related to anti-TB drugs. So due vigilance is needed while patient is on ATT so that patient can complete the treatment and get cured which can be beneficial for the society too. Limitation of the study is that it is a single centre study on few patients. Larger studies directed towards specific population are required before generalizing findings of this study to whole community.

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