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AN OBSERVATIONAL STUDY ON ADVERSE DRUG REACTIONS AMONGST PATIENTS RECEIVING ANTI TUBERCULAR DRUGS AT GMERS HOSPITAL, GANDHINAGAR

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ABSTRACT: Tuberculosis treatment requires multidrug regimens have been associated with increased incidence of adverse drug reactions (ADRs). This study aimed to determine incidence, risk factor and pattern of adverse drug reactions in patients receiving anti-tubercular drug. This was a prospective observational ADR monitoring study conducted on in-patient & out-patient department of TB & chest, GMERS Hospital, Gandhinagar. The suspected ADR found was assessed for its severity and Causality. The obtaineddata were analysed and represented as number and percentage. Data was descriptively analysed byusing graph pad prism. A total of 48 patients with suspected ADR were included as they matched the inclusion & exclusion criteria. Frequency of different ADRs was assessed and p value was determined. A total of 104 ADRs were identified and reported from 48 patients showing an overall incidence of 10.34% with male being the most affected than female. The patients with age group of 18-40 were most commonly affected with ADRs (50%). The patient with low BMI, History of Diabetes, HIV or other co-morbidities, life-style habits are on risk of developing ADR. Gastrointestinal tract (57.69%) were most affected with ADRs. Most of the ADRs were caused due to combination of all four drugs. The majority of reactions (52.88%) were found to have "Possible" causal relation with drug. About 57.76% ADRs observed were "Moderate" in severity. Out of 104 reported ADRs, 34(32.69%) ADRs were totally recovered. ADR monitoring is an effective tool in identifying and assessing suspected reactions both with outpatients and inpatients. Thus an extensive ADR monitoring and reporting system should be adopted in every hospital which helps them to ensure patient safety through detection of new, serious and rare adverse drug reactions.

KEYWORDS: DOTS therapy, adverse drug reactions, Tuberculosis, Pharmacovigilance, Anti-tubercular therapy.

I. INTRODUCTION

Undoubtedly modern drugs have increased life expectancy and provided quality of life to millions of people. However, despite all these benefits, evidence continues to suggest that adverse drug reactions due to medicines are common, though often preventable, cause illness, disability, and sometimes even death. [1] The World Health Organization (WHO) defines an ADR as "a reaction which is noxious and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis or therapy of disease or modification of physiological function. [2] Adverse Drug reactions are a major cause of morbidity and mortality.

Worldwide approximately 5% (ranges from 2% - 20%) of reported hospitalizations are because of an ADRand at least one ADR has been reported to occur in 10-20% of a hospitalized patients. In many countries, ADRs rank among the top 10 leading causes of mortality and India is one of them. [3] Tuberculosis (TB) is caused by bacteria of the *Mycobacterium tuberculosis* complex. It is one of the oldest diseases known to mankind and was as well as still been responsible for a huge death toll worldwide. India is the country with the highest-burden of TB.[4] The World Health Organization (WHO) statistics for 2017 give an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 10 million thus making

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India accountable for almost one-third of the global TB burden.[5]

Directly observed treatment, short course (DOTS) was introduced in India in 1993 as part of Revised National Tuberculosis Control Programme (RNTCP), following a review of India's NTP a year earlier. The key component of DOTS therapy is the standard anti-TB short course chemotherapy regimen, which requires continually taking drug combinations of isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA) and ethambutol (EMB) every other day for 6-9 months. [6]
Despite the positive therapeutic effects, studies have shown that utilization of multidrug regimens can cause undesirable adverse drug reactions (ADRs) of varying degrees of severity, such as hepatotoxicity, gastrointestinal (GI) disorders, allergic reactions, arthralgia, neurological disorders, and so on. Ability of tubercle bacilli to acquire resistance to ATT is very high. ATT have high range of adverse effects. Hence to decrease the resistance and adverse drug reactions, combination of drugs is used. [7]

Studies suggest that more than 5% of the patients on anti-tubercular drugs (ATD) develop ADRs. [8] None of the anti-TB drugs is without adverse reactions only rarely are the adverse reactions life-threatening. ADRs can be a potential factor leading to treatment non-adherence. [9] This further causes development of resistant strains requiring second line therapy of drugs with higher cost and more serious ADRs. It is well recognized that anti-tubercular drugs are associated with severe adverse effects leading to economic burden and decreased quality of life.

The high prevalence of TB treatment highlight the need of the importance of the clinical pharmacist, for monitoring ADRs and to increase awareness of ADRs among the patients and health care professionals by reporting any suspected ADRs. This type of activity of the pharmacist will help in minimizing ADRs. [10][11] There is no extensive published data regarding the adverse effects of anti-tubercular drugs in this setting.

The current study was conceived to monitor suspected ADRs with anti-tubercular drug, frequency and pattern of ADRs to contribute to the overall knowledge base regarding ADRs in the country. The present study aims to understand the incidence, risk factor and pattern of adverse drug reactions in patients receiving anti-tubercular drug.

II. Material and Methods

Study design & Site:
A Prospective, Observational ADR monitoring study conducted at In-patient department (IPD) and Out-patient department (OPD) of TB and chest, GMERS Hospital, Gandhinagar, Gujarat.

Study duration:
The study was carried out for a period of 6 months; 4 months of data collection and 2 months of evaluation & analysis (October 2019 to March 2020).

Selection and description of participants:
Study Population:
Patients visiting IPD and OPD of TB & Chest receiving anti-tubercular drug with a suspectedADR during the period of data collection.

Sample Size:
Convenient sample size that matches both inclusion and exclusion criteria during the timeframe period.

Study Eligibility criteria:
Inclusion Criteria:
- Patients receiving anti-tubercular drug with suspected ADR (suggested by physician), with or without other comorbid condition; both new cases, on-going and relapse cases.
- Patient of either sex with age more than 18 years
- All the patients observed with suspected ADR and provided with written signed informed consent will be included in the study.

Exclusion criteria:
- Patients who are unwilling to participate and did not give consent in the study.
- Patient with incomplete medical record.
- Patient with MDR-TB.
- Pregnant women.

Study Materials
Informed consent form- English and Gujarati language. The patient information sheet in English and Gujarati language had been provided to the patient which explains them about the study procedures in brief. An informed consent was signed before entering the patient into the study as a proof of voluntary participation.

Suspected ADR reporting form- Suspected ADR reporting form version (2.1) adopted by IPC was used in its original form only for documenting the details of reported suspected ADR.

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Study tools for ADR Assessment and Analysis

a) *Naranjo's Causality Assessment Scale*

b) ADR Severity Assessment scale (Modified Hartwig and Siegel-1992)

c) Extended Rawlins and Thompson

d) Classification of ADR.

Study Procedure:

(1) Approval-

Ethics Committee Approval:

The study was started after ethics committee approval from Institutional Ethics committee of the GMERS Medical College & KBIEC- K.B. Institute Ethics Committee, K. B. Institute of Pharmaceutical Education and Research, Gandhinagar.

(2) Data collection procedure-

Patient were first screened according to the inclusion and exclusion criteria and eligible patient were explained regarding the study procedure and informed consent was taken prior to the enrolment of patient in study. On routine consultation of patient in TB-Chest OPD and IPD, if Physician suspects to have a reaction associated with prescribed drugs then it was reported to the study investigators for further data collection. All the ADR relevant information of the patients were collected from patient's by interviewing patient, reviewing case file, progress report, laboratory data and were transcribed into the CDSCO Suspected ADR reporting form. Information regarding Patient Demographics, Suspected drug & observed adverse reactions, Concomitant Medications, Relevant History and Laboratory test were recorded. The follow up of reported reaction after management were done via telephonic interviews with TB-Chest outpatients while it was done through clinical interview on daily basis for inpatients throughout hospitalization.

(3) Data management and analysis:

The collected Data were analyzed for its causality with suspected drug using Naranjo's Algorithm, severity of reaction using Hartwig & Sheigel Scale.

Once the causal relation was established, each reaction was classified using Extended Rawlins and Thompson classification of ADR & outcomes of reactions are noted. The results obtained after the data analysis were recorded and transferred in CDSCO Suspected ADR Reporting form appropriately.

Statistical Analysis:

The data was subjected to statistical analysis using Microsoft Excel and Graph Pad Prism, Windows Version 10. Categorical variables such as patient's gender, type of tuberculosis, treatment regimen, treatment duration and others expressed in frequencies and percentage. Numerical data such as age expressed in mean. Socio-demographic, lifestyle and habits patients that may related to adverse drug reactions occurrence was analysed using chi square test at 95% confidence interval using graphpad prism. The p value < 0.05 will be considered as significant.

III. Results

Adverse drug reactions due to antitubercular therapy are expected to be present in a majority of the patients as part of the multi drug combinations or due to the disease process. During the study period a total of 464 patients on antitubercular therapy, of which 48 patients met the study criteria that were experienced one or more ADR which was induced by anti-tubercular drugs. The mean age observed in our study were 41.05 years ± 14.22. Amongst 48 patients, 24 (50%) patients were between the age group of 18-40 years, 16(33.3%) patients were between 41-60 years of age while the other 8 (16.6%) patients age 60 years above. Age and Gender wise distribution is shown in Table 1.

Occurrence of ADR was more in male patients. Out of this, 33 (69%) were male and 15 (31%) were female. Chi square test result for gender and ADRs occurrence showed p-value 0.20 (>0.05), means that patients gender is not affected with ADRs occurrence. Related to ages, chi-square test result showed p-value less than 0.05 (0.99), it means that age is also not related to ADRs occurrence.

Out of 48 patients developed ADRs, 46 (95.83%) were having pulmonary TB and rest 2 (4.17%) had extrapulmonary TB. No statistically significant association was found between gender of patient, site of TB and occurrence of ADRs (p>0.05). Drug combination used on intensive phase among tuberculosis patient included in this study can also be seen on table 1. The table also showed that combination of isoniazid, rifampicin, ethambutol, and pyrazinamide are mostly used on patient as much as 29 (60.41%) of total patients. This table showed that 21 (43.75%) patients are in continuous phase.

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There are 5 (10.41%) patients determined with HIV and 43 (89.58%) not determined with HIV. Tuberculosis patients with diabetes mellitus as co-morbidity are in 6 (12.5%) patients and patients with other disease as co-morbidity are 8(16.66%).

According to habit and lifestyle, there are 17 (35.41%) Tobacco chewer, small number on alcohol use 11(22.91%), and only 5(10.41%) patients smoker patients. ADRs occurrence related to smoking status, alcohol use and drug abuse can also be seen in Table 1.

Total 104 ADRs were suspected and reported in 48 Patients. Overall incidence of ADR was found to be 10.34%. Out of 48 patients the percentage of patients with single and more than 1 ADR was 37.5% and

Table 1: Risk Factor Associated with Developing ADRs

Sr. No.	Variable	No. of Participants		Chi square	P value	AOR (95% CI)
		ADR present (n= 48)	ADR Absent (n=416)			
1	**Gender**					
	Male	33	249	1.428	0.2	1.476 (0.7771 to 2.802)
	Female	15	167		NA	1.00 Reference
2	**Age**					
	18-39	24	208		NA	1.00 Reference
	40-59	16	139	0.000049	0.99	1.002 (0.5153 to 1.955)
	>60	8	69	0.00012	0.99	0.9952 (0.4273 to 2.318)
3	**BMI**					
	Underweight	40	347		NA	1.00 Reference
	Normal	8	54	0.3689	0.5436	0.7781 (0.3456 to 1.751)
	Overweight	0	15	1.722	0.1895	3.613 (0.2102 to 61.87)
4	**TB History**					
	New	39	280	3.89	0.048	2.10 (0.9909 to 4.471)
	Relapse	9	136		NA	1.00 Reference
5	**Type of TB**					
	Pulmonary	46	399	0.00070	0.97	0.97 (0.2193 to 4.379)
	Extra Pulmonary	2	17		NA	1.00 Reference
6	**Treatment Phase**					
	IP	29	252	0.1238	0.72	0.89 (0.4956 to 1.1630)
	CP	21	164		NA	1.00 Reference
7	**HIV**					
	Yes	5	97	4.176	0.04	0.38 (0.1473 to 0.9925)
	No	43	319		NA	1.00 Reference

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62.5% respectively. The majority case of adverse drug reactions is gastro intestinal reactions such as nausea & vomiting 25(24.03%), Gastritis 14(13.46%), Abdominal pain 9 (8.65%) and anorexia 9(8.65%) followed by Generalised weakness and flu like syndrome in 6 (5.77%) patients.

All adverse drug reactions that occurred among tuberculosis patients can be seen in Table 2. In this study the majority of reactions occurred within four weeks of treatment followed by within sixteen-twenty weeks, within eight weeks and less number of reactions observed in treatment period of one week and thirty weeks. This can be seen in Table 3.

The maximum number of ADRs found affecting gastrointestinal system i.e. 60(57.69%) followed by Whole body as a general system (n=14, 13.46%). The least found affected systems were Musculo-skeletal system and Neuro-psychiatric system (01 ADR, 0.96% each). This can be seen in Table 4.

Causality assessment of ADRs with drug helps to prevent future recurrence of harm. The causality assessment of ADRs revealed that 46cases (44.23%) were detected as probable and 58 (55.76%) as possible (Table 5). Evaluation of the severity of ADRs indicated that 42.30% of the ADRs were mild and 57.76 were moderate (Table 6). 2.88 % were severe cases. Severity of ADR is decided based on the extent of harm to patient and clinical intervention required to manage the ADRs. Mild ADRs require no or minimum intervention, while moderate reactions requires considerable intervention and severe ones need continuous monitoring.

Out of the 104 ADR observed, only 3 reactions required complete stoppage of that offending agent, while 16 reactions require interruption of treatment and most of the reactions (43, 41.34%) were

Table 2: Pattern and Frequency of ADR

Name of Reaction	No. of Patient	Frequency of ADR (%) (n=104)
Nausea and Vomiting	25	25 (24.03%)
Gastritis	14	14 (13.46%)
Abdominal pain	9	9 (8.65%)
Anorexia	8	9 (8.65%)
Generalised weakness	6	6 (5.77%)
Flu like syndrome	6	6 (5.77%)
Hepatotoxicity	4	5 (4.80%)
Headache	5	5 (4.80%)
Ulcer	4	4 (3.84%)
Itching/Rash	4	4 (3.84%)
Arthralgia	4	4 (3.84%)
Icterus/Jaundice	3	3 (2.88%)
Peripheral neuritis	3	3 (2.88%)
Increase in LFT	2	2 (1.92%)
Anaemia	1	1 (0.96%)
Mental confusion	1	1 (0.96%)
Optic Neuritis	1	1 (0.96%)
Diarrhoea	1	1 (0.96%)
Oedema	1	1 (0.96%)

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managed with supportive medication without removing anti tubercular drug from their treatment regimen.(table 7). Among the 104 ADRs, 34 (32.69%) reactions were totally recovered, 22 (21.15%) were recovering and 47 (45.19%) still continuing in the patient. There were only one fatal outcomes of reported ADRs in this study. (Table 8)

Table 3: Onset of ADRs reported

Duration of Onset	No. of ADR (N=104)
Within one week (7 days)	15
Within four weeks (28 days)	25
Within eight weeks (56 days)	15
Within sixteen weeks (112days)	18
Within Twenty weeks (140 days)	19
Within thirty weeks (210days)	12
Total	104

Table 4: Classification of organ system affected with ADR

Organ System	No. of ADR (%) N=104
GIT	60 (57.69%)
Whole body as a system	14 (13.46%)
Hepatobiliary	9 (8.65%)
Nervous system & special senses	8 (7.69%)
Skin & appendages	7 (6.73%)
Musculo-skeletal	4 (3.84%)
Metabolic and nutritional	1 (0.96%)
Neuro-psychiatric	1 (0.96%)

Table 5: Causality Assessment of ADR

Causality (Naranjo score)	No of ADR (%) (n=104)	Average Naranjo Score
Definite (>9)	0 (0%)	0
Probable(05- 08)	46 (44.23%)	5.30
Possible(01- 04)	58 (55.76%)	3.93
Unlikely (<0)	0 (0%)	NA

Table 6: Severity Assessment of ADR

Severity	No of ADR (%) (n=104)
Mild (Level 1& 2)	43 (41.34%)
Moderate (Level 3& 4)	58 (57.76%)
Severe (Level 5, 6 & 7)	3 (2.88%)

Table 7: Management of ADR

Measures taken for suspected drug	No. of ADR (%) (N=104)
Symptomatic therapy with -out Withdrawal	43(41.34%)
Drug Regimen continued	38(36.53%)
Drug Regimen withheld	16(15.38%)
Dose Regimen adjustment	4(3.84%)
Drug Regimen Stopped	3(2.88%)

Table 8: Outcome of the ADR

Outcome of the reaction	No. of ADR (%) (N= 104)
Continuing	47(45.19%)
Recovered	34(32.69%)
Recovering	22(21.15%)
Death/fatal	1(0.96%)
Unknown	0(0%)
Other	0(0%)

IV. Discussion

An adverse drug reaction is a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. A general knowledge about ADRs is essential for effective management of any disease.[12] Tuberculosis requires prolonged treatment and some of the drugs may cause ADRs involving the GIT, liver, skin, nervous system, Otto-vestibular apparatus and eyes. One of the common reasons responsible for noncompliance to RNTCP guidelines aredevelopment of ADRs. Therefore, it becomes important to study the profile of ADRs and itsoutcome. [13]

In our study, we found that the current incidence of side effects was 10.34%, in a total of 48 patients on the similar lines study from which is slightly lower than study conducted in a chest clinic at,Malaysia by Fivy et al.2010[14] found the incidence of ADR to be 15.8%. Literature review of several study reveals that the incidence of ADR ofanti-tubercular drugs ranges from 7.79% to 58.26% [13, 15]

In the present study majority of the ADRs were reported by the age group 18-40 years (50%). This is probably because the people in this age group are involved in TB infectious activities like smoking, large alcohol intake etc. which results in the weakening of immunity. [16] This is in accordance with Supriya et al. [12] It seems that patient demographic characteristics mostly are age between 18-40 years old & male. This is in accordance with Anusha et al. [17]

In our study, males had a higher incidence of ADRs that is 11.70% as compared to Females 8.24%. It may be due to the fact that the males are having higher risk factors like smoking, alcoholism, and drug addiction to get TB than females and men are socially more active and visit public places more often. These risks make them more vulnerablefor TB infection. [17] This is in accordance with Anusha et al. [17] and in contrast with Mahendra et al. [18]

According to Evidence, females are considered to be more at risk of ADRs due to their smallerbody size and body weight compared to males. A study by Sachin *et al*.,[15] and Supriya *et al*.,[12]have tried to consolidate this fact that female gender is a risk factor for the occurrence of ADRsdue to anti-TB drugs due to smaller body size, less body weight, low socio-economic status, poor nutrition, immunological and hormonal factors, differences in pharmacokinetic parameter and lack of awareness about medication.[18] But as the male (n= 282) constitutes more no. of subjects than female (n=182), so naturally male (33 out of 282, 11.70%) contributed to ADRs more than female (15 out of 182, 8.24%).

Co-presentation of TB with other communicable and non-communicable diseases is considered as an important risk factor for result of more ADRs. Co-morbidity can drastically weaken the immune system.[19] Occurrence of ADRs was significantly associated with History of TB infection, co-morbidities with HIV & diabetes, and habit of smoking and tobacco chewing in this study which was also supported by other studies and literature.[18,20]

Appearance of the ADRs is an important factor as some of them appeared very early and othersdelayed. In our study about 25% of the ADRs occurred within the first month of therapy.In the study by Dhingra,[12] 67% of the ADRs occurred in the first four weeks. The average lagin start of treatment and appearance of adverse drug reaction was immediate reaction to 120 days. As some of the ADRs would appear early and would gradually increase while others present only in the initial period and gradually subside with passage of time.

Since DOTS is a combination therapy, it is very difficult to find a causal relationship between individual drug and ADE without de-challenging it, which was done only in one patient. Even in this study, in three cases drug were stopped, and risk of re-challenge was not found feasible. This indicates that a close monitoring and follow-up of patients is essential for initial month for early detection and prevention of serious ADRs. This information should help the prescriber to remain vigilant during this period and also educate the consumers. Interestingly, gastrointestinal system alongwith liver and biliary system are the common targets for serious ADRs. Despite gastrointestinalADRs with 57% frequency, no patient quit DOTS-Plus therapy. Insistence on treatmentcontinuation by HCPs and family could be an important factor for this. Our observation are synonymous with Kinjal et al. [7]

Management to ADRs occurrence mostly with add on medication, then followed by withholding the medication regimens, continue without change and the last is change patient'streatment regimens. Add on medication in 43 (41.34%) patients, is the most common step to manage adverse drug reactions especially in gastro-intestinal reaction, the clinicians add on antiemetic for relieving nausea and vomiting, Proton pump inhibitor for Gastritis and Pyridoxine 100 mg for peripheral neuropathy. Metronidazole was given in the patients with diarrhea. Add on medication such as antihistamine agent for reducing minor skin reactions. Anti-pyretic like acetaminophen was given for the flu like syndrome and headache. Folic acid was given for the mouth ulcer. Then in some cases the clinicians stop the drugs (withhold) when severe reactions appeared, this in 16 (15.38%) patients.

In our study, if increase in liver enzymes was seen first step clinician took was to discontinue the drugs until the reaction resolved after that identify the causative agents by rechallenging (restarting) each drug in order of Ethambutol with levofloxacin followed by rifampicin, isoniazid and pyrazinamide. This is similar to the study conducted by the Fivy et al.[14] and Dayanand et al.[21]

Since the study period was limited for only for months with small sample size though the value of its result cannot be ignored. However, a large scale observational study with larger sample size along with longer follow-up period could have provided with better rate of incidence database for TB drug regimen associated ADRs. The patients who stay in far villages often do not report to us for minor side effects. Though we tried to contact them regularly telephonically they may not have reported minor side effects.

II. CONCLUSION

All anti-tubercular drugs trigger one or more ADRs which may lead to non-adherence and had shown many unpleasant affects in TB patients. This creates the importance of close monitoring of patients who were at higher risk of getting ADRs. The age group of 18-40 and male populations showed higher incidence who developed ADRs. Most common ADR was GI symptoms but most were moderate and most severe reaction were hepatotoxicity. Patients with risk factors should be carefully monitored during the anti-tuberculosis drug treatment (DOTS strategy). A comprehensive clinical history (smoking and body mass index) and additional exams might be useful to identify these patients.

In this study we observed that inpatients were observed with more Adverse reactions due to the complex prescribing patterns in them. This present findings are beneficial as they give an idea about the pharmacovigilance system in the hospital and its working pattern. Our sample size though small and limited to just a single site, is enough to implicate that larger comparative studies are essential. The activity of the pharmacovigilance needs to be strengthened.

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