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ORIGINAL ARTICLE

THE ANTITUBERCULAR DRUG INDUCED ADVERSE EFFECTS IN REGISTERED CASES UNDER RNTCP – DOTS, PROGRAMME IN BIJAPUR

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ABSTRACT: AIM: The aim of this study is intended to make an effort to determine the incidence of adverse effects and the risk factors for developing side effects against anti-TB drugs. **DESIGN**: Prospective study. **MATERIALS & METHODS**: The present study was carried out in the Department of Pulmonology, Shri B M Patil Medical College BLDE University, Bijapur, Karnataka, during the period from May to July 2012. The 50 newly diagnosed tuberculosis patients who fulfilled below stated criteria were selected during the study period, attending at RNTCP Nodal center at Shri B M Patil Medical College, Hospital were included in the present study. **STATISCAL ANALYSIS**: Categorical variables such as patient's gender and others expressed in frequencies and percentage. Numerical categories such as age expressed in mean. Socio demographic, lifestyle and habits patients that may related to adverse drug reactions occurrence was analyzed with frequencies and percentages. **RESULTS**: A total of 50 newly diagnosed tuberculosis patients taking Anti-tuberculosis treatment during the time period from 14th may 2012 till patients who developed at least one adverse drug reaction were noted and the details entered in the patient profile form, for the study14th July 2012 were taken up for analysis. Adverse drug reaction Reporting Form recorded with all the essential information regarding the adverse effects. All tuberculosis patients were reviewed at first two week after started treatment and thereafter every month, except if they have an experience of adverse drug reactions, they were informed to visit the doctor immediately. **CONCLUSION**: Incidence of Adverse Drug Reaction (ADR) of Anti-tuberculosis treatment is high, majority of the reported ADR were graded as mild and did not need modification of the treatment. Females had a high incidence of ADR.

KEYWORDS: TB (Tuberculosis), RNTCP (Revised National Tuberculosis Control Programme), DOTS (Directly observed Treatment Short course), ADR (Adverse Drug Reaction).

INTRODUCTION: Tuberculosis (TB) is caused by organisms belonging to the Mycobacterium tuberculosis complex.[1] The World Health Organization (WHO) declared TB as a global emergency in 1993.[2] It has been reported by WHO that one third of the world's population is infected with Mycobacterium tuberculosis resulting in 8.4 million new tuberculosis cases in 1999.[3] This high incidence of infection has caused a large number of morbidity and mortality which is partly due to serious adverse reactions induced by Anti-TB drugs.[4, 5]

WHO has defined Adverse Drug Reaction (ADR) as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[6] Some common ADR due to the anti-tubercular drugs are visual disturbances, peripheral neuropathy, jaundice, skin rashes, pancreatitis, hyperuricaemia, ototoxicity and hypersensitivity reactions.[7]The studies have found that ADR account for 5%of all hospital admissions and cause death in 0.1% of medical and 0.01% of

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surgical cases.[8] It has been found that 50% of the ADR are preventable in the first place.[9] In view of the high prevalence of TB and widespread use of antitubercular drugs, it has become the need of the hour to monitor for ADR and increase awareness of ADR among consumers in the population.

Hence, the present study was carried out with the objectives, to study the ADR pattern due to first line anti-tubercular drugs used in DOTS in Bijapur, Karnataka India.

MATERIALS AND METHODS: Study type: Prospective study. Study site: The present study was carried out in the Department of Pulmonology, Shri B M Patil Medical College, Hospital and Research Centre BLDE University Bijapur, Karnataka, during the period from May to July 2012. The 50 newly diagnosed tuberculosis patients who fulfilled below stated criteria were selected during the study period, attending at RNTCP nodal center at Shri B M Patil Medical College, Hospital and Research Centre, were included in the present study. Inclusion and exclusion criteria: All the patients who developed adverse drug reactions which were documented in the files were included in the study. Patients with impaired renal or hepatic dysfunction, uncontrolled medical conditions like severe anemia, congestive heart failure, Ischemic Heart Disease and the files of the patients which were not located and without proper documentation and unwilling to give written consent were excluded from the study.

Institutional Ethical Clearance: The study was approved by Institutional Ethical Clearance Committee of Shri B M Patil Medical College, Hospital and Research Centre, Bijapur Karnataka and informed consent was taken from the patients. Operational modality: The files of all the TB patients who received treatment during the time period from 14th may 2012 till 14th July 2012 were taken up for analysis. The chest physician reviewed the files thoroughly and looked for any documented adverse drug reactions. All the patients who developed at least one adverse drug reaction were noted and the details entered in the patient profile form, for the study. The filled patient profile forms were analyzed for results. The various study tools used were the patient profile form which recorded all the information, such as name, age, sex, socioeconomic status, life style factors and dietary factors and any concurrent diseases and medications other than antitubercular agents that the patients might be taking.

Adverse drug reaction Reporting Form recorded with all the essential information regarding the adverse effects like the onset and severity experienced its impact on the treatment and work capacity of the patient, the drug(s) involved, the date of starting the suspected drugs and the date of reporting of the adverse drug reaction. Regular visits to the RNTCP DOTS center were made by us during the study period. Drug regimens Treatment was planned as recommended by our National Tuberculosis control Programme (NTP) and patients were given Directly Observed Treatment, Short course (DOTS) by medical staffs of the clinic.

According to the national protocol, patients with a new diagnosis of TB receive 6 months of Anti-tuberculosis treatment consisting of 2 months of rifampin (R), isoniazid (H), ethambutol(E) and pyrazinamide (Z) followed by 4 months of R and H (2RHEZ/4RH). Information on any past or current occurrence of adverse effects due to the antituberculosis drugs being administered to them was collected from the patients directly by the researchers. However, in very few cases, the responses were obtained from the attendants in the absence of the patient. The results obtained were then compared with those documented in the literatures.

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thereafter every month, except if they have an experience of adverse drug reactions, they were informed to visit the doctor immediately.

Incidence of Adverse drug reactions was determined from the rate of adverse reaction cases obtained from population beginning anti-TB therapy. The intensity of the reported ADR will be graded as follows: Grade 1 -Transient or Mild discomfort; no limitation in activity; no medical intervention/therapy required, Grade 2 - Mild to Moderate limitation in activity; some assistance may be needed; no or minimal medical intervention / therapy required, Grade 3 - Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalizations possible and Grade 4 - Extreme limitation; significant assistance required; significant medical intervention / therapy required; hospitalization, according to Naranjo ADR probability scale.[10] Data analysis: Categorical variables such as patient's gender and others expressed in frequencies and percentage. Numerical categories such as age expressed in mean. Socio demographic, lifestyle and habits patients that may related to adverse drug reactions occurrence was analyzed with frequencies and percentages.

RESULTS: A total of 50 patients were included in the study among these patients 24 developed at least one ADR giving an incidence of 48%.Among them 38 (76%) were males and 12 (24%) were females shown in table 1. Table 2 gives the incidence of ADR among which females (75%) were found having higher incidence than males (39.47%). Patient demography: The mean ± SD age of the patients developing ADR is 45.26±13.45 years. The demography of the patients who developed ADR listed in table 3. The association of lifestyle factors considered as risk factor for occurrence of ARDs listed in table 4. Altogether a total of 84 ADR were experienced and details are listed in table 5.Majority of the ADR were related to central nervous system 18(21.42%) That is tingling and burning sensation in hands and feet 12(14.29%) and headache 06(7.14%). Most (90.48%) of the reported incidences of ADR were graded as mild and 9.52% as moderate.

The association of incidence of ADR and different parameters is studied and possible predisposing factors found were age (the age group 41-60) years was seen to have maximum incidence of ADR (45.83%) and the age group (0-20) years had lowest reported incidence (0.00%), sex (there was higher prevalence of ADR in females 75% than in males 39.47%). No association between gender and occurrence of ADR was found by statistical analysis.

No association of occurrence of ADR was found with life style and dietary factors (maximum ADR were reported by non-smokers, non-alcoholics, non-users of chewing tobacco and non-vegetarian patients. Among 24 patients, 12 patients (50%) experienced ADR within 20 days 02 (8.33%) in 21-40 days, 05 (20.8%) within 41-60 days and the remaining 06 (25%) in more than 60 days after starting the treatment. In our study 90.48% of patient showed mild ADR around 9.52% showed moderate ADR and none of them showed severe reaction, which explained in table 6. The majority of the reported ADR in our study are categorized as "possible" as per the Naranjo signs and symptoms were enquired.

No dechallenge and rechallenge was done to establish the causative agent, placebo effect was not studied, and no laboratory investigations were done to determine the concentration of the drug in body fluids and tissues. Owing to lack of all these parameters, none of the reported ADR could be classified as 'definite' attributed to the suspected drugs. Thus the most possibly suspected drugs causing them are shown in table 7.

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SL. NO	Parameters	Frequency	Percentage (%)
01	Male	38	76
02	Female	12	24

Table 1: Sex distribution

Sl. No	Sex	No. of patients (%)			
		Developed ARDs		Not developed ARDs	
		Reports	Percentage (%)	Reports	Percentage (%)
01	Male	15	39.47%	23	60.52 %
02	Female	09	75%	03	25%

Table 2: Occurrence of ADR in males and females

Sl. No	Age Group (years)	No. of Patients (%)			
		Developed ARDs		Not developed ARDs	
		Reports	Percentage (%)	Reports	Percentage (%)
01	0-20	00	0.00	01	3.85
02	21-40	09	37.5	12	46.15
03	41-60	11	45.83	11	42.31
04	>60	04	16.67	02	7.69

Table 3: Age Distribution

Sl. No	Parameters		No of Patients			
			Developed ARDs		Not developed ARDs	
			Reports	Percentage (%)	Reports	Percentage (%)
01	Smoking status	Former smokers	10	41.66	09	34.62
		Current smokers	01	4.17	03	11.54
		Non smokers	13	54.17	14	53.84
02	Alcohol Consumption	Former alcoholics	09	37.5	07	26.92
		Current alcoholicis	01	4.17	01	3.85
		Non alcoholic	14	58.33	18	69.23
03	Tobacco chewing	Former users	02	8.33	03	11.54
		Current users	03	12.5	02	7.69
		Non users	19	79.17	21	80.77
04	Dietary Factor	Vegetarians	10	41.67	12	46.15
		Non vegetarians	14	58.33	14	53.85

Table 4: Association of life style factors considered as risk factors for occurrence of ADR

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Sl. No	Adverse Drug Reactions Noted	No. Of Cases	Percentage (%)
01	Tingling & burning sensation in hands & feet	12	14.29
02	Nausea / vomiting/ Anorexia	10	11.9
03	Itching with / without rash07	09	10.71
04	Epigastric distress	09	10.71
05	Joint pains	08	9.52
06	Muscle pain / back pain/ body ache	08	9.52
07	Vertigo / dizziness	07	8.33
08	Headache	06	7.14
09	Weakness	05	5.95
10	Diarrhoea	02	2.38
11	Constipation	02	2.38
12	Shortness of breath on mild exertion	02	2.38
13	Cough	02	2.38
14	Dim vision	01	1.19
15	Burning sensation in eyes	01	1.19

Table 5: Types of Adverse Drug Reactions experienced by the patients

Sl. No	Severity	No. of reports	Percentage (%)
01	Mild	76	90.48
02	Moderate	08	9.52
03	Severe	00	0.00

Table 6: Severity of ADR

Sl. No	Suspected drugs	No. of reports	Percentage (%)
01	Isoniazid	30	35.71
02	Pyrazinamide	15	17.86
03	Rifampicin	38	45.24
04	Ethambutol	01	1.19

Table 7: Suspected drugs causing the ADR in the patients on ATT

DISCUSSION: A total of 50 patients were enrolled in this study among which 24(48%) developed ADR due to anti-tubercular drugs. This result is much higher than the result of the study by Kishore PV et al,[11] found to occur only in 12.27% of cases developed anti-tubercular drug induced ADR.

As they mentioned their study was carried out in western Nepal population, the difference in the results might be because this study was retrospective one and hence certain minor ADR might have not been documented. In another study carried out in Nepalese population by Chhetri AK et al, [12] reported by 54.74% of anti-tubercular drug induced ADR, the difference in results could have resulted due to the genetic, demographic and nutritional status differences among the two populations.

In a study by Dhingra VK, et al,[13] reported by 8.37% of anti-tubercular drug induced ADR in

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Delhi population. Female patients experiencing ADR were more in our study than the male patients.

The two studies Rajni Shakya et al[14] and Dinesh Koju et al[15], showed the occurrence of the side effects from Anti-Tuberculosis Drugs in Urban Nepalese Population Under DOTS Treatment, female gender as a risk factor for the occurrence of ADR due to anti-TB drugs. Generally, females are considered to be more at risk of ADR due to their smaller body size and body weight compared to males or it might be because females pass through life stages like pregnancy, menarche etc., which modify the drug response.

However, our study failed to establish the association between gender and incidence of an anti-tubercular drug induced ADR. In our study majority of the ADR were reported by the age group 41-60 years. This result is in contrast to the Chhetri AK et al[12] findings where age group 21-40 years was associated with increased incidence of ADR due to anti-tuberculosis drugs. The studies by Daphne Yee et al[16] and T. Schaber et al[17], where age over 60 years was associated with increased incidence of ADR due to anti-tuberculosis drugs. Rajni Shakya, et al.[14]

Showed that patients belonging to the younger age group 21-40 years were found to be at higher risk for anti-tuberculosis drugs induced hepatotoxicity. In our study, no laboratory investigations were done to detect asymptomatic hepatotoxicity. From the different life style factors the most reported ADR in this study were associated with non-smokers, non-alcoholics, non-users of chewing tobacco and non-vegetarians. However, these findings are in accordance with Chhetri AK et al.[12] The result of Dinesh Koju et al,[15] Occurrence Of The Side Effects from Anti-Tuberculosis Drugs in Urban Nepalese Population Under DOTS Treatment, has concluded that the risk factors associated with increased occurrence of major side effects included old age, female sex, alcoholics and Sputum-smear positive. In our study, current alcoholics and smokers were very few and no specific laboratory investigations were done to detect asymptomatic hepatic toxicities.

These reasons could have caused the difference in results seen in our study and those reported in other studies. Statistical analysis also could not establish any significant association between the various life style factors and the incidence of ADR. The majority of the ADR reported in this study were categorized as 'possible' as per the Naranjo's algorithm signs and symptoms were enquired.[10] No dechallenge or rechallenge was done to establish the causative agent, placebo effect was not studied, and no laboratory investigations were done to determine the concentration of drug in body fluids or tissue. Owing to the lack of all these parameters, none of the reported ADR could be classified as 'definite' attributed to the suspected drugs. In this study, (21.42%) of ADR reported involved the central nervous system.

The highest reported ADR was peripheral neuropathy, characterized by a tingling and burning sensation in the hands and feet (14.29%). INH was considered to be the suspected drug responsible for peripheral neuropathy. This conclusion was made based on the literature evidence suggesting maximum incidence of peripheral neuropathy due to this drug Zaoui A et al.[18] The other anti TB drug known to cause peripheral neuropathy is Ethambutol, but very rare in comparison to INH. The most common system affected by ADR due to anti-tuberculosis drugs was hepatobiliary. In a study by Dhingra VK et al,[13] in New Delhi on ADR due to Anti-tuberculosis drugs majority of the patients (53%) had gastrointestinal disturbances, the commonest being nausea and vomiting.

The result of their study could also have been different because majority of the patients undergoing treatment at the RNTCP DOTS center were of lower socioeconomic status and could have been malnourished. Among the reported ADR in our study, (90.48%) was classified as mild ADR and

(09.52%) as moderate ADR as per the Grading scale mentioned in the result. Mild ADR requiring no change or intervention in treatment with the suspected drug occurred in 76 patients (90.48%).

Among the 8 patients (9.52%) with moderate ADR. Onset of the ADR is an important factor helpful in early detection of the ADR. In our study, half of the ADR occurred within the first 20 days of the initiation of ATT. Also in a study by Kishore PV et al,[11] 52.5% of the ADR occurred in the first 20 days of the initiation of ATT.

It is essential for the healthcare professionals to counsel the patients regarding the early identification of ADR in the first few weeks. Regular monitoring of the patients during these initial weeks might be essential for early detection of ADR.

CONCLUSION: Incidence of ADR of Anti-tuberculosis treatment is high, majority of the reported ADR were graded as mild and did not need modification of the treatment. Females had a high incidence of ADR.

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