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Original Research Article

A study of adverse drug reactions among pulmonary tuberculosis patients treated under dots in a tertiary care hospital

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ABSTRACT

Background: DOTS under RNTCP is the current treatment available for Pulmonary Tuberculosis. This treatment exhibit a greater level of efficacy with a small degree of toxicity. The present study aims to determine demography of patients with pulmonary tuberculosis and to study the ADRs caused by anti tubercular drugs and to assess the causality and severity of the reported ADRs.
Methods: We studied cases of Pulmonary Tuberculosis diagnosed and treated under category I DOTS at Department of Pulmonary Medicine for the period of one year (during 2015). Adverse effects observed during treatment course were recorded in standard 'Adverse Drug Event Reporting Form'. ADRs were also assessed for their causality and severity by using WHO-UMC criteria and Hartwig's scale.
Results: Pulmonary cases accounted for 67.6% of total TB cases. Among 434 cases of pulmonary tuberculosis 33 (7.6%) patients were defaulters; among them 3(9.5%) cases were defaulters due to ADRs. In our study 96 patients developed 123 ADRs of various types and most of the ADRs noted within first 2 weeks of initiation of treatment. Gastritis was the most common ADRs (28/22.7%) followed by anorexia (26/21.1%).
Conclusions: In our study 22.1% of patients developed ADRs. ADRs recorded in our study were categorised under 'probable' and 'possible' causes and severity assessment showed 48% are moderate and 52% are 'mild' in nature. Still ADRs accounted for 9% default rate. Hence implementations of good patient care oriented programs are needed for early diagnosis and to reduce default rate and drug resistance.

Keywords: Hartwig's scale, Naranjo's causality assessment scale, Pulmonary Tuberculosis

INTRODUCTION

The WHO declared TB as a global health emergency in 1996.[1] Tuberculosis is a major public health problem in India. Our country bear the burden of one-fifth of the global TB incident cases and topping the list.[2] As per WHO estimate, 9 million people globally develop active TB and 1.7 million die of it annually.[3] It is estimated that annually around 330,000 Indians die due to TB.[4]

Pulmonary tuberculosis is the most common presentation of tuberculosis disease, mode of spread being droplet inhalation. Mycobacterium may spread to any organ of the body through lymphatic or haematogenous dissemination and lie dormant for years at a particular site before causing disease. Manifestations may relate to the system involved, or simply as prolonged fever and nonspecific systemic symptoms.

Treatment of Tuberculosis was a challenge for clinicians in the past. After many studies it was concluded that multiple drugs and prolonged treatment is the key for successful treatment. DOTS was introduced in 1993 in India as part of RNTCP.[5] One of 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), Ethambutol (EMB), and/or Streptomycin (SM) every other day for 6-9 months.[6]

Though ATT has good therapeutic effects, studies have showed these multidrug regimens can cause undesirable

adverse drug reactions (ADRs) of varying degrees of severity, such as allergic reactions, gastrointestinal (GI) disorders, hepatotoxicity, neurological disorders, arthralgia and so on.[7-10] A study done by Chukanov et al suggests that more than 5% of the patients on anti-tubercular drugs (ATT) develop ADRs.[11] None of the anti-TB drugs is safe but rarely these ADRs are life threatening. A study done by Awofeso N showed ADRs can be a potential factor leading to treatment non adherence.[12] ADRs increase patient suffering and incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations. [9] So close monitoring of adverse drug reactions and its effective management is needed. Pharmacovigilance activities can help in obtaining real information of safety and effectiveness of medicines when they are being used in the population.[13]

Most of the time treatment of ATT induced ADRs are conservative. For Minor side effects treatment should be continued with symptomatic measures such as antacids, antihistamines, antiemetics, or analgesic. If major side effects occur, the regimen or the offending drug if identified must be stopped. Further management depends on the nature of side effects and may have to be done in a hospital.[14]

The present study aims to determine the presentation and outcome of patients with pulmonary tuberculosis treated with category I DOTS and to identify the incidence and pattern of ADRs caused by anti tubercular drugs and to assess the causality and severity of the reported ADRs.

METHODS

Data was collected from cases of Pulmonary TB diagnosed at Sri Siddhartha Medical College Hospital and Research centre, Tumakuru during the year 2015 that are treated under DOTS. Demography of these patients was recorded. Treatment outcome was evaluated as cured, completed treatment, defaulted, failed, or died based on the definitions given by the WHO.

Inclusion Criteria for this study includes all cases of Pulmonary TB of all age groups and both sexes treated at our centre. Exclusion Criteria includes any cases of Drug resistant TB, Diabetes Mellitus, Ischemic Heart Disease, Chronic Kidney Disease and HIV co-infection, and Patients on cat II ATT and patients with previous history of allergy to anti-tubercular drugs.

All the patients of pulmonary tuberculosis were enrolled after taking their informed consent and monitored for ADRs. Patient profile was maintained to identify the patient demography, date of start and completion of treatment, record of follow-up, and incidence of ADRs, onset, management and outcome of the ADRs. Any adverse effects observed were recorded in the 'Adverse Drug Event Reporting Form' prepared by the CDSCO, Govt. of India. ADRs were also assessed for their causality and severity as per the standard algorithms. 434 cases were studied for ADR monitoring during the study period and causality was assessed using world Health Organization –Uppsala monitoring centre (WHO-UMC) and Naranjo's causality assessment scale. Severity was assessed by Hartwig's questionnaire.

The study was conducted after obtaining ethical clearance from institutional ethical committee. The statistical analysis was done by using descriptive analysis.

RESULTS

We subjected 2145 suspected cases for investigation to rule out tuberculosis during the year 2015. Among them 752 cases of TB were diagnosed. They were further classified as Sputum Positive Pulmonary TB (n=456), Sputum Negative pulmonary TB (n= 53) and Extra-pulmonary TB (n=243). Pulmonary TB cases accounted for 67.6% of total cases (Table 1).

Table 1: Total number of pulmonary and extra-pulmonary cases.

Total number of TB suspected cases	Total number of cases of pulmonary TB		Total number of Extra-pulmonary cases diagnosed
	Number of sputum positive cases	Number of x-ray positive, smear negative cases	
2145	456 (60.6%)	53 (7.04%)	243 (32.2%)

After inclusion and exclusion criteria 434 cases of Pulmonary TB cases were included in the study. Among them 285 (65.6%) were male and 149 (34.4%) were female patients and most of the patients were in the age group of 20-40 years (Table 2).

Table 2: Age and sex distribution of pulmonary TB cases.

Age	Sex		Total
	Male	Female	
< 20 years	63	46	109
21-40 years	155	67	222
41-60 years	52	29	81
>60 years	15	07	22
Total	285 (65.6 %)	149 (34.4%)	434

Among 434 cases of Pulmonary tuberculosis who were on DOTS treatment, 382 (88%) patients completed treatment, 33 (7.6%) patients defaulted, 14 (3.2%) patients died and there were 05 (1.2%) cases of treatment failure (Table 3). Out of 33 defaulters, the most common reason for defaulting treatment was irregular treatment 12 (36.3%), alcohol abuse 14 (42.4%) and 3 (9.5%) was due to ADRs (Table 4).

Table 3: Treatment outcome of total subjects.

Treatment outcome	Results (number of patients)	Percentage (%)
Treatment completed	382	(88%)
Defaulted	33	(7.6%)
Died	14	(3.2%)
Failure	5	(1.2%)
Total	**434**	**(100%)**

Table 4: Reasons for Default.

Reason for default	Number of patients (%)
Irregular treatment	12 (29.5%)
Alcohol	14 (23.5%)
Refused DOTS drugs	4 (11.7%)
Stopped due to ADRs	3 (9.5%)
Total	**33 (100%)**

Our study revealed that out of 434 patients, 96 patients developed 123 ADRs of various types. Among them, most of ADRs were observed in males (68/70.8%) and remaining (28/29.2%) among females. The overall incidence of ADRs was 22.11%.

We categorized ADRs according to the systems affected like gastrointestinal system, skin, nervous system and other systems like vestibular system, musculo-skeletal system etc. Majority of ADRs were related to gastrointestinal system (67 cases) followed by central nervous system (20 cases), skin (9 cases) and other systems (27 cases). Gastritis was the most common ADR (28/22.7%) followed by anorexia (26/21.1%), weakness (18/14.63%), Hepatitis (13/10.56%), peripheral neuropathy (11/8.9%) and skin reactions (9/7.3%) (Figure 1). Among 95% of the cases, the suspected drug was continued in spite of the ADR, without any complications.

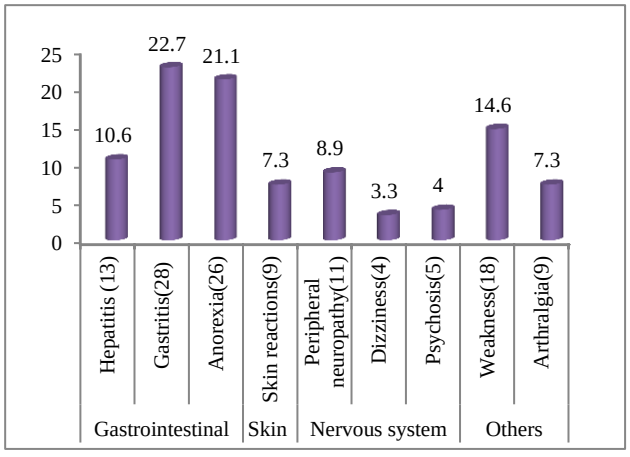

Figure 1: The figure depicts the frequency of distribution of adverse drug reaction to Anti-Tubercular drugs.

We studied onset of ADRs during the course of treatment. 13 (10.5%) cases of the ADRs occurred on the first day of the treatment and 43 (34.9%) ADRs occurred within a week of treatment, 56 (45.5%) in the second week, 11 (8.9%) in the third week of the initiation of anti tubercular therapy.

Causality assesment of ADRs, revealed majority of them were found to be probable (52%) followed by possible (42%) (assessed as per WHO-UMC and Naranjo's scales). The Naranjo algorithm is used widely in the causality assessment of ADRs. It is based on the score calculated on the basis of points assigned to each of the ten questions that comprises the table. These ADRs were classified into different levels like mild, moderate or severe based on the Modified Hartwig and Siegel scale. The severity assessment of ADRs showed that 48% reactions were moderate and 52% were of the 'mild' in nature as per the Hartwig et al scale.

DISCUSSION

We studied 2145 suspected cases of tuberculosis at our site during the year 2015. Among 752 cases of TB diagnosed, 456 had Sputum Positive Pulmonary TB, 53 had Sputum Negative pulmonary TB and 243 had Extra-pulmonary TB. Sputum positive Pulmonary TB accounted for 60.6%, Sputum negative Pulmonary TB 7% and extra-pulmonary cases accounted for 32.2% of total TB cases. Our study is in consistent with study done by chandir.s.[17] In the present study tuberculosis was seen more in males compared to females. Similar results were seen in other studies.[18,19] However, Mir Azam Khan reported equal number of cases in both sex.[20]

Among 434 cases of Pulmonary tuberculosis studied, 382 (88%) patients completed treatment, 33 (7.6%) patients defaulted, 14 (3.2%) patients died and there was 05 (1.2%) case of treatment failure. Similar study conducted by Chandir S showed higher Default rate (34.5%) and only 59.8% patients had completed treatment and more treatment failures (5.2%) compared to our study and finally 3.2% patients died during treatment in this study.[17]

The most common reason for default in our study was irregular treatment (36.3%) followed by alcohol abuse (42.4%) and ADRs (9%). Chandrashekaran reported illiteracy, alcohol intake and smoking as the causes for default.[21] The study by Tekle reported that default was 11.3%, the reason being lack of family support, inadequate knowledge of treatment duration and side effects of medication. [22]

Out of 434 patients enrolled in the study, 96 patients developed 123 ADRs (22.1 %). The highest number of ADRs (68/70.8%) was observed in males which are in contrast to the study by Yee and Shakya et al which showed female gender as a risk factor for the occurrence of ADRs due to anti-TB drugs.[23] But in the study, by

D.K.Tak et al, males developed more ADRs, which could be due to majority of males included in the study.[24]

In our study, 331 patients were under 40 years of age (76.2%) followed by 81 patients at age of 40-60 (18.66%) and 22 were in more than 60 years age group (5%). This result is in contrast to the study by Yee et al where age over 60 years was associated with increased incidence of ADRs due to anti TB drugs. A study conducted by Daphne et al showed that ADRs due to anti tubercular drugs occurred in patients above the age of 60 years. But in our Study, majority of ADRs were observed in patients below 60 years of age. This may be due to less number of patients in above 60 yrs age group in our study. We noted 115 (93.5%) cases of ADRs in patients less than 40 years and 40-60 years of age group.

In our study we timed ADRs during treatment course. We noted 13 (10.5%) of the ADRs occurred on the first day of the treatment 43 ADRs (34.9%) occurred within a week of treatment, 56 (45.5%) in the second week, 11 (8.9%) in the third week of the initiation of anti tubercular therapy. Most of the ADRs were noted before 2 weeks of initiation of treatment. So intensive monitoring for ADRs required during first two weeks of treatment. We suggest educating patients regarding side effects of these drugs and when to report to doctor and arrange for a follow up visit between 1-2 weeks after initiation of treatment.

The highest reported ADR was gastritis 28 (22.7 %) which is in accordance to the study by Dhingra et al, where it was around 53%.[9] Anorexia was the second common ADR noted 26(21.1%). A study conducted by Sainul Abideen P et al reveals that, GI system, liver and biliary system is the most frequent organ system affected by ADRs.[13] Multiple drug therapy was noticed to be a major predisposing factor for developing GI side effects.

Other ADRs noted were generalised weakness, Hepatitis and Peripheral neuropathy in our study population, whose occurrence was comparable to that found in the study conducted by Dhingra et al.[9]

On evaluation of the causality of ADRs, a majority of the reactions were probable (52%), followed by possible (42%). There were no definite reactions. Gholami et al also supported the same findings that the probable reaction was the more.[15]

The reported ADRs were classified into different levels like mild, moderate or severe based on the Modified Hartwig and Siegel scale. The severity assessment of ADRs showed that 48% reactions were moderate and 52% were of the 'mild' nature as per the Hartwig et al scale. A study by Gholami et al shows similar result in which most of the adverse drug reaction are of moderate severity.[15] A study by Tak D K also supported this result.[16]

CONCLUSION

This study was conducted to analyse Pulmonary TB cases and to look for ADRs of ATT in our hospital. Pulmonary Tuberculosis accounted for predominant type of TB (67.6%) With good percentage of patients completed treatment (88%). Our study revealed 33 (7.6%) default rate. Treatment irregularities and alcohol abuse and ADRs are the three most common reasons for default. The side effects may steer the patient to make a judgment for stopping the medications and finally the occurrence of drug resistance and leading to amplified health care cost. We noticed more number of ADRs in males possibly due to more male patients in the study. Gastro-intestinal system was the most common system involved in ADRs. Most of the ADRs reported in our study were categorized as mild to moderate severity. In majority of the cases, ATT was continued in spite of the ADRs, without any complications. Most of the ADRs were noted within 2 weeks of initiation of treatment. So intensive monitoring for ADRs required during first two weeks of treatment. Hence implementation of good patient care oriented program is need of the hour and arrange for a follow up visit before 2 weeks of initiation of treatment.

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