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A Study on Assessment of Adverse Drug Reactions in Tuberculosis Patients.

K.V. Ramanath[1*], Ramesh.S[1]

1. Department of Clinical Pharmacy, Sri Adichunchanagiri College of Pharmacy, B G Nagara, Nagamangala Taluk, Mandya District, Karnataka ,Pin-571448, India.

ABSTRACT

The present study was carried out to monitor, estimate the prevalence and consequences of ADRs on treatment of TB and to assess causality, predictability, preventability and severity of the ADRs. A prospective observational and active surveillance study was conducted over a period of 9 months. Each reported ADR was assessed for its causality, severity, predictability and preventability as per standard algorithms. The management and outcome of ADRs were determined. A total of 128 ADRs (in 53 patients) were identified out of which the prevalence of ADRs in female was found to be 31.58% and 29.66% in male patients. The causality assessment by Naranjo's scale showed that out of 128 ADR's, 128 (100%) ADR's were probable and based on WHO probability assessment scale 119(92.97%) were possible where as 9(7.03%) were probable. Preventability assessment showed that 125 (97.66%) were not preventable and 03 (2.34%) were definitely preventable. Severity Assessment by Modified Hartwig and Siegel Scale showed that 82 (64.06%) ADRs were mild and 46(35.94%) ADRs were moderate. 128(100%) were found to be predictable. Majority of the ADRs were recovered without giving symptomatic treatment. The study concluded that there is a need of a system for proper monitoring of ADRs caused by anti-TB drugs in RNTCP centre. The counselling of patients for timely prevention, detection and management of ADRs will helps in further ADR occurrence minimisation.

Keywords:

Adverse drug reactions, Tuberculosis, World health organisation, Directly Observed Treatment-Short course (DOTS), Revised National Tuberculosis Control Programme (RNTCP).

*Corresponding Author Email: kattavenkateshramanath@gmail.com

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INTRODUCTION

Infectious diseases are the important leading causes of death (morbidity and mortality) among the people of Tuberculosis (TB), HIV/AIDS and with other chronic diseases.[1] Among various infectious diseases, TB is one of the leading contagious infection responsible for death which is affected by *Mycobacterium tuberculosis.*[2]

Out of 22 high burden countries of TB, the 5 countries rankings are - India (1.98 million), China (1.3 million), South Africa (0.47 million), Nigeria (0.45 million) and Indonesia (0.43million). Out of 9.4 million global annual TB cases, 1.98 million were estimated/occurred in India (2008), in which 0.87 million were caused because of an infectious disease which made a path to fifth global burden disease.

Almost 70% of TB patients are aged between the ages of 15 and 54 years of age in both the genders. Whereas two third cases are male. The disproportional of occurring this disease in females also more.[3]

In 1993, WHO declared TB as a global emergency and National Tuberculosis Programmes (NTPs) strategy was started all over the world to employ the daily regimens/ Directly Observed Treatment-Short course (DOTS) of anti-TB drugs. [4] Because of an Expert Committee opinion Revised National Tuberculosis Control Programme (RNTCP) was framed for the entire country to sort out the lacunas. In DOTS, patients are grouped into two categories and are treated with four to five anti-tubercular drugs intensively and chronically based on the category.

Long duration of TB treatment drugs like Isoniazid, Pyrazinamide, Rifampin, Ethambutol and Streptomycin – are potentially responsible to cause adverse drug reactions like hepatotoxicity, visual disturbance, arthralgia, headache, skin rashes etc. These Adverse reactions mostly observed/occur in the first three months of treatment.[5]

According to WHO, Adverse Drug Reaction (ADR) is "Any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function".[6] The study of ADR field is known as pharmacovigilance. According to WHO, pharmacovigilance is the science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems.[7]

In India pharmacovigilance is not widely practice, due to this, Ministry of Health and Family Welfare, Govt. of India, with WHO funding, initiated a country wide National Pharmacovigilance Program (NPV) on 23rd November, 2004 at New Delhi. Under this

programme, the Central Drugs Standards Control Organization appointed the central co-ordinating body for 2 zonal, 5 regional and 24 peripheral centres. The objective of this programme is to create awareness among the health care professionals on ADR monitoring and to encourage a reporting culture.[8]

The high prevalence of TB treatment makes/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 helps in minimizing ADRs.[9, 10]

A large number of patients are exposed to anti-TB drugs at PHCs of RNTCP/DOTS, yet no such major findings were observed in monitoring/detecting of ADRs. The ADRs are the one of the major reasons for patient default about their treatment. [11,12] Hence, the present study was carried out in RNTCP/DOTs center with the objectives to monitor, estimate the prevalence, consequences of ADR on treatment and to assess causality, predictability, preventability and severity of the ADRs.

MATERIALS AND METHODS

The study was a prospective observational and active surveillance study was conducted in the Adichunchanagiri Institute of Medical Sciences and Research Center, B G Nagara and RNTCP/DOTS centers within the TB unit of Mysore city (8 centers) over a period of 9 months. Ethical clearance and permition was obtained from the Institutional Human Ethical Committee of Adichunchanagiri Hospital and research center (AHRC) and SAC College of Pharmacy, B G Nagara and Mysore district TB officer for conducting of this study.

The TB treatment card helps in getting the information on patient demographic details like age, weight, type of TB, HIV status, date of start of therapy, phase of treatment, date of completion of therapy, history of previous anti-TB therapy, further information regarding co morbid conditions and ADR experienced by the individual patient can be obtained by interviewing the patient.

All the patients from the selected sites who are on DOTS treatment either in continuous phase / were newly DOTS started were enrolled into the study after obtained their consent. All the required information received by the patient was documented in the suitably designed piloted patient data collection form. When suspected ADRs are detected, they were brought to the notice of the medical officer for further evaluation. Details regarding the suspected drug, date of suspected drug started, date of onset of reaction, brief description of the reaction were documented in the suspected ADR notification form and authenticated by the in charge medical officers signature and date of reporting.

All the information present in the suspected ADR notification form was documented in the data assessment form for assessing the causality, predictability, preventability and severity. All the identified ADRs were assessed for causality using the WHO ADR probability scale and Naranjo's algorithm,[13,14] predictability by using predictability scale, severity by Modified Hartwig and Siegel scale[15] and preventability by Modified Schumock and Thorton criteria.[13] The documented data was subjected for descriptive statistical analysis.

RESULTS AND DISCUSSION

A total of 128 ADRs were observed/ noticed in 53 patients out of totally 175 enrolled patients. The prevalence of ADRs in females was 31.58% and 29.66% was in male patients Table-1. The ADRs were more prevalent at the age group of 41 to 50 years i.e., 41.38% Table-2 and in underweight patients i.e., 34.17%. In our study findings, the prevalence of ADRs was observed more in non-alcoholics i.e., 32%, former/past smokers i.e., 32.9% and former/past tobacco users i.e., 32.26%. The prevalence of ADRs was found to be more in the patients with the history of previous anti-TB treatment i.e., 40%, intensive phase (category –I) 46.53% and Category II (continuous phase) 42.11%. Patients with co morbidities like DM were more prevalent to ADRs i.e., 85.71%. The patients who are receiving Isoniazid, Rifampicin, Pyrazinamide and Ethambutol were found with more number of ADRs i.e., 40 (75.5%) when compare with other combinations. The number of suspected ADR percentage prevalence in 53 patients showed in the order of 17(32.1%) ,15(28.3%),12(22.6%),4(7.5%), 3(5.7%),2(3.8%) respectively in Figure 1.

Table 1: Details on distribution of prevalence of ADRs based on Gender wise

Gender	Number of patients (%)	Number of patients with ADR (%)	% Prevalence
Male	118 (67.4)	35 (66.04)	29.66
Female	57 (32.6)	18 (33.96)	31.58
Total	175 (100.0)	53 (100.0)	

Table 2: Details on distribution of ADRs in TB patients based on age and its prevalence

Age in years	Number of patients (%)	Number of patients with ADR (%)	% Prevalence
1-10	04 (2.3)	00 (0)	00
11-20	14 (8.0)	04 (7.54)	28.57
21-30	39 (22.3)	12 (22.64)	30.77
31-40	53 (30.3)	15 (28.30)	28.30
41-50	29 (16.6)	12 (22.64)	41.38
51-60	27 (15.4)	07 (13.21)	25.93
61 & above	9 (5.1)	03 (5.67)	33.33
Total	175 (100.0)	53 (100.0)	

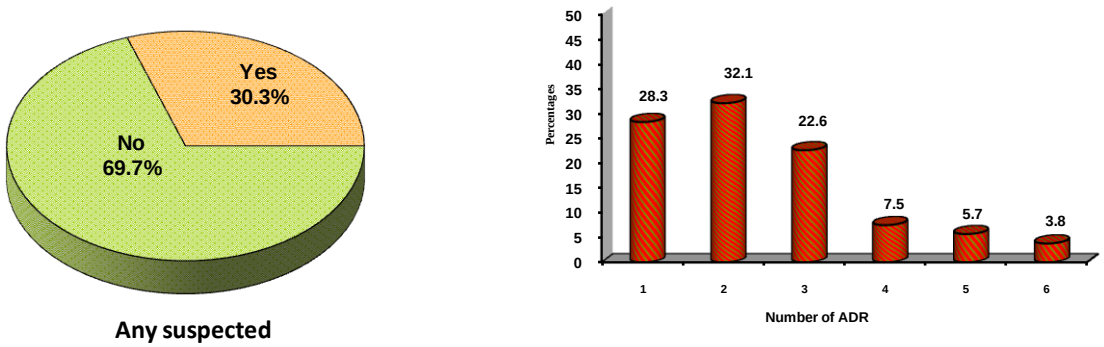

Figure 1: Suspected ADR and Number of ADRs percentage

Table 3: D**etails on distribution of types of ADRs occurred based on System wise**

System organ class	No. of ADRs (%) (n=128)	No of patients with ADRs (%) (n=175)
Gastro-intestinal system disorders	31 (24.22)	25 (14.29)
Vomiting	11 (08.59)	11 (6.29)
Nausea	15 (11.73)	15 (8.57)
Diarrhoea	01 (0.78)	01 (0.57)
Abdominal pain	01 (0.78)	01 (0.57)
Heart burn	02(1.56)	02 (1.14)
Flatulence	01 (0.78)	01 (0.57)
Skin and appendages disorders	35 (27.34)	29 (16.57)
Pruritis	27 (21.09)	27 (15.43)
Rash	08 (06.25)	08 (4.57)
Musculoskeletal system	30 (23.44)	22 (12.57)
Arthralgia	15(11.72)	15(8.57)
Myalgia	15(11.72)	15(8.57)
Central and peripheral nervous system disorders	28(21.88)	23 (13.14)
Dizziness	10 (7.81)	10 (5.71)
Headache	10 (7.81)	10 (5.71)
Neuropathy	08(06.25)	08(4.57)
Vision disorders	04(03.12)	04 (2.29)
Blurred vision	04(03.12)	04(02.29)

ADR's affecting the Skin and appendages were high i.e., 27(21.09%), while ADR's affecting other systems were as follows Gastro intestinal system i.e., 15(11.73%), Musculo skeletal system i.e., 15(11.72%), Central and peripheral nervous system i.e., 10(7.81%), Vision i.e., 4(3.12%). The most commonly identified adverse drug reactions affecting Skin were pruritis i.e., 27 (21.09%) followed by rashes i.e., 08 (06.25%), Gastro intestinal system were nausea i.e., 15 (11.73%), followed by vomiting i.e., 11 (08.59%), heart burn i.e., 02 (1.56%), diarrhoea, abdominal pain, flatulence i.e., 01 (0.78%**),** Musculo skeletal system were arthralgia and myalgia i.e.,15(11.72%), Central and peripheral nervous system disorders were dizziness, headache i.e.,

10 (7.81%) followed by neuropathy i.e., 08(06.25%) and Vision was blurred vision i.e., 04(03.12%). Table-3

Assessment scales

Causality assessment was done by using both Naranjo's and WHO scale. The assessment by Naranjo's scale showed that out of 128 ADR's 128 (100%) ADR's were categorised as probable. The WHO scale assessment revealed that out of 128 ADR's 119(92.97%) were possible and 09(7.03%) were probable. Preventability assessment showed that 125(97.66%) were found to be not preventable and 3(2.34%) ADRs were found to be definitely preventable. The severity assessment showed that 81(63.28%) were found to be mild level 1, 01(0.78%) were mild level 2 and 46(35.94%) were found to be moderate level 3. Based on predictability scale, 128(100%) were found to be predictable. Table-4

Table 4*:* Details on distribution of type/category of ADRs according to various assessment scales

ADR assessment scales	Number of ADRs (n=128) (%)
Causality: Naranjo algorithm	
Probable	128 (100.0)
Possible	00 (0)
Causality: WHO scale	
Probable	09 (7.03)
Possible	119 (92.97)
Severity scale	
Mild – level 1	81 (63.28)
Mild – level 2	01 (0.78)
Moderate – level 3	46 (35.94)
Predictability Scale	
Predictable	128 (100.0)
• Incidence	125 (97.66)
• History of exposure	02(1.57)
• Incidence and history of exposure	01 (0.78)
Non-predictable	00 (0)
Preventability scale	
Preventable(Definitely preventable)	03 (2.34)
Not preventable	125 (97.66)

Even though ADR occurred there is no change in treatment but stopped in only one patient due to fatal severity. Maximum people were observed with ADR, because of this moderate severity of ADR observed in some patients were administered with supportive treatment (ex: antihistamines, NSAIDs), remaining ADRs are subsided after sometime. In our study the ADR's were most commonly associated with patients receiving HRZE 40(75.5%), HE 9(16.9%), HR

8(15.1%), HRZES 7(13.2%) and RES, RZ, R were 4(7.5%).Table-5 Majority of the ADRs occurred are resolved followed by improved and continuing Table 6.

Table 5: Details on distribution of name of suspected drug(s) responsible for ADRs

Suspected drug(s)	Number of patients (n=53)	%
HRZS	1	1.9
RZ	4	7.5
HRZES	7	13.2
HRZE	40	75.5
HE	9	16.9
R	4	7.5
HR	8	15.1
RES	4	7.5

H - Isoniazid, R- Rifampicin, Z- Pyrazinamide, E- Ethambutol, S- Streptomycin

Table 6*:* Details on distribution of Outcome of ADR

Outcome of ADR	Number of ADRs (n=128) (%)
Continuing	26 (20.31)
Improved	43 (33.6)
Recovered	59 (46.1)
Total	128 (100.0)

The study have some limitations like laboratory investigations to determine plasma or tissue drug concentrations, liver function tests, haematological tests, serum uric acid or acetylator status of the patients were not done, because of expensive and data obtained from interview of the patient's family(low level educator) sometimes may not able to get the complete data.

CONCLUSION

This study showed that the prevalence of ADRs was high (30%) with first line anti-TB drugs (DOTs therapy). Majority of the patients felt that after taking their treatment the condition become worsening, but truly speaking which is caused due to ADR of ATT, this shows wrong conception about treatment. This was minimised by clinical pharmacist involvement in interviewing the patient and counselled to meet the medical officer, thereby encouraging the DOTS provider (pharmacist/ health care professional) to address the problem. This study concluded that there is a need of a close monitoring system for proper detection of ADRs caused by antiTB drugs. Counselling of patients for timely prevention, detection and management of ADRs will helps in minimising the further occurrence of ADR.

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