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Original Research Article

The study of adverse drug reactions in indoor patients of tuberculosis taking standardized antitubercular therapy (directly observed treatment short-course and programmatic management of drug resistant tuberculosis) in a tertiary care hospital at Surat

Payal P. Naik^{1*}, Arvindsingh Panwar¹, Swati Patel²

¹Department of Pharmacology, ²Department of Community Medicine, Surat Municipal Institute of Medical Education and Research (SMIMER), Surat, Gujarat, India

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***Correspondence:**

Dr. Payal P. Naik,

Email: naikpayalp@yahoo.co.in

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ABSTRACT

Background: Tuberculosis is a serious public health issue in India. The treatment regimen followed is Directly observed treatment short-course (DOTS) and Programmatic Management of Drug resistant Tuberculosis (PMDT) approach. In a long period of treatment adverse drug reactions (ADRs) can be an important programmatic issue. Thus, study was undertaken to assess the ADRs caused by antitubercular therapy in indoor patients in a tertiary care hospital at Surat.

Methods: The Observational, prospective study was carried out for one year period. The causality was determined by WHO UMC scale and severity was determined by Modified Hartwig and Siegel scale. Chi square test was applied for statistical analysis.

Results: Among 255 tuberculosis patients, 85 (33.3%) patients developed ADRs. Occurrence of ADRs was more among females (46.6%). The commonly involved systems are gastrointestinal (40.6%) followed by haematological (17.9%). The most common ADRs observed were nausea and vomiting (21.7%). High percentage of ADRs causing drugs were isoniazid (30.6%) followed by rifampicin (26.1%). Causality assessment showed 60.4% ADRs were possible, 37.7% ADRs were probable and 1.9% ADRs was certain. Severity assessment scale showed 81.1% of moderate, 12.3% of mild and 6.6% of severe grading. Occurrence of ADRs was more among PMDT (60%) in comparison to DOTS therapy (31.06%) [p value = 0.0084 (significant p value < 0.05)].

Conclusions: Antitubercular treatment is safer but early detection, management and reporting of ADRs is required to prevent it at initial stage and helps to decrease default rate.

Keywords: Adverse drug reaction, DOTS, PMDT, Antitubercular drugs

INTRODUCTION

Tuberculosis is a grave public health issue with high morbidity and mortality. It is due to bacterial infection named as *Mycobacterium tuberculosis* complex.¹ The incidence of tuberculosis cases were 2.2 million have been estimated in India in the year 2015.²

The Revised National TB Control Programme (RNTCP) was established in 1993 and it is based on Directly observed treatment short-course (DOTS). In India the treatment regimen followed for tuberculosis is DOTS approach as Category I, Category II and Programmatic management of drug resistant tuberculosis (PMDT) approach as Category IV, Category V.

DOTS therapy includes drug combinations of isoniazid, rifampicin, pyrazinamide, ethambutol and/or streptomycin for 6-9 months period. While PMDT includes combinations of various second line drugs regimens. Multi drug resistant TB patients are treated with a standardized six drug (Category IV- ethionamide, cycloserine, levofloxacin, kanamycin, ethambutol and pyrazinamide) for 24-27 months regimen. The Extensively Drug Resistant cases are treated with (Category V) for up to 30 months daily regimen.³

Adverse drug reaction (ADRs) defined as any noxious, unintended and undesired effect of a drug which occurs at a dose used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions.³ It is important issue while dealing with defaulters.

Various studies have shown that multidrug regimen can cause ADRs such as hepatotoxicity, gastrointestinal (GI) disorders, arthralgia, dermatological reactions, neurological disorders etc.⁴⁻⁹ It may lead to noncompliance and non-adherence to therapy. Thus patients remain infectious for longer period of time which increase the risk to the community. This further causes development of resistant strains requiring second line therapy with higher cost and serious adverse drug reactions.

Therefore, it is necessary to monitor and treat ADRs by DOTS and PMDT therapy. There are few studies available regarding ADRs of PMDT therapy.¹⁰

Thus to assess the ADRs caused by antitubercular drugs in our setup, we have planned this study.

METHODS

This was Observational and prospective study in patients who were taking DOTS and PMDT therapy (indoor patients) in Respiratory Medicine department in SMIMER hospital located at Surat. The study was carried out for one year period comprising of data collection and data analysis later on.

Ethical approval

Informed verbal and written consent was taken from patient and relative after persuading the participants about the possible benefits and implications of the study. Strict confidentiality of their personal details was maintained.

Sample size calculation

Sample size calculated by considering the proportion of ADRs in patients by two weeks pilot survey (indoor patients of Respiratory Medicine department) is 16.12%.

$$n = Z^2 \alpha \div 2pq \div l^2$$

$$= 85$$

Where $p = 16.12\%$ or 0.1612 , $q = 1-p$, $l =$ allowable error $= 8\%$,

$$Z \alpha/2 = \text{level of Confidence} = 95\% = 1.96$$

Inclusion criteria

Patients with 18 years and above age group were included in the study. Indoor patients who were ready to give written informed consent were included in the study. In case of patient's inability his/her parents or guardians consent was taken.

Exclusion criteria

Patients below 18 years of age group. Uncooperative patients who had not given written informed consent or on refusal of giving consent from parents or guardians. Pregnant / lactating women. With liver / kidney disease. Alcoholic patients. Patient with concurrent illness (HIV, diabetes, hypertension) or receiving medication for it.

On the working days we went to the Respiratory Medicine ward and interviewed the patients to get detailed information about their clinical status, past history, possible adverse effects, management of disease and ADRs. Information collected in a proforma. All decisions related to management of the patient including drugs and investigations were taken by the pulmonologist only. Events were considered as ADRs with combined opinion of investigator and pulmonologist. In case of difference of opinion, pulmonologist's opinion was considered final. The causality of the ADRs was determined using WHO UMC scale. The severity of the ADRs is determined using Modified Hartwig and Siegel scale.

Statistical analysis

Chi square test was applied to know association between two variables at 5% level of significance.

RESULTS

A total of 440 indoor patients suffering from tuberculosis were enrolled in the study. Among them 255 patients satisfied our inclusion criteria. Out of this 85 (33.3%) patients were reported with ADRs.

The proportion of tuberculosis was more in males (71.4%) as compared to females (28.6%). While occurrence of ADRs was more among females (46.6%) as compared to males (28.1%). Gender is not associated with DOTS and PMDT therapy. [p value =0.1620, OR = 2.835 (0.688, 8.259)] (Table 1).

The proportion of the disease was more among patients below 40 years of age (69.4%) as compared to those above 40 years of age (30.6%). But occurrences of ADRs were comparable in both groups. i.e. (33.9%) and (32.05%) (Table 2).

Majority 58 (68.2%) of the patients with ADRs belonged to weight below 40 kg. There is no statistical difference of weight in relation to DOTS and PMDT. [p value =0.8348, OR=0.6806 (0.1687, 2.746)] (Table 3).

Table 1: Adverse drug reactions among patients on antitubercular therapy as per gender.

Gender	No. of patients as per inclusion criteria	No. of patients developed ADRs	(%) of occurrence of ADRs
Male	182 (71.4%)	51 (60%)	28.1
Female	73 (28.6%)	34 (40%)	46.6
Total	255 (100%)	85 (100%)	33.3

Table 2: Adverse drug reactions among patients on antitubercular therapy as per age.

Age	No. of patients as per inclusion criteria	No. of patients developed ADRs	(%) of occurrence of ADRs
<40 years	177 (69.4%)	60 (70.6%)	33.9
>40 years	78 (30.6%)	25 (29.4%)	32.05
Total	255 (100%)	85 (100%)	33.3

Table 3: Adverse drug reactions among patients on DOTS and PMDT therapy as per body weight.

Weight (kg)	No. of patients on DOTS	No. of patients on PMDT	Total	(%) of occurrence of ADRs
<40	49 (84.48%)	09 (15.52%)	58	68.2
>40	24 (88.89%)	03 (11.11%)	27	31.8
Total	73	12	85	100

Out of 85 ADRs reported patients, 72 (84.7%) belonged to pulmonary tuberculosis and 13 (15.3%) belonged to extrapulmonary tuberculosis. Among them 43 (50.6%) patients were on Category I regimen, 30 (35.3%) were on Category II regimen, 7 (8.2%) were on Category IV regimen and 5 (5.9%) were on Category V regimen.

The commonly involved systems are gastrointestinal system 43 (40.6%) followed by haematological system 19 (17.9%), liver and biliary system 16 (15.1%), central and peripheral nervous system 8 (7.5%), musculo-skeletal system 11 (10.4%), auditory system 6 (5.7%) and dermatological disorder 3 (2.8%) (Figure 1).

Table 4: Distribution of adverse drug reactions as per causative drug.

List of drugs causing ADRs	No. of patients	Percentage
Isoniazid	41	30.6
Rifampicin	35	26.1
Pyrazinamide	22	16.4
Ethambutol	5	3.7
Streptomycin	18	13.4
Kanamycin	3	2.23
Ethionamide	5	3.7
Capreomycin	2	1.5
Amikacin	1	0.7
Levofloxacin	1	0.7
Cycloserine	1	0.7
Total	134	100

Table 5: Distribution of adverse drug reactions based on severity of reactions.

Severity of ADRs	Frequency	Percentage
Death	01	0.9
Life threatening	03	2.8
Hospitalization/ Prolonged stay	50	47.2
Required intervention to prevent permanent impairment/ damage	06	5.7
Non serious	46	43.4
Total	106	100

Table 6: Causality assessment as per WHO UMC scale for adverse drug reactions.

Grading	Frequency	Percentage
Possible	64	60.4
Probable	40	37.7
Certain	2	1.9
Total	106	100

Table 7: Severity assessment using Modified Hartwig and Siegel scale.

Grading	Frequency	Percentage
Mild	13	12.3
Moderate	86	81.1
Severe	7	6.6
Total	106	100

Commonly identified ADRs from gastrointestinal system included nausea and vomiting 23 (21.7%), followed by gastritis 10 (9.4%), diarrhoea 6 (5.7%) and constipation 4 (3.8%); from haematological system included hypokalemia 16 (15.1%) followed by anaemia 3 (2.8%); from liver and biliary system included hepatitis 16 (15.1%); from central and peripheral nervous system included insomnia 3 (2.8%), peripheral neuropathy 2 (1.8%), psychosis 1 (0.9%),

headache 1 (0.9%), hallucination 1 (0.9%); from musculo-skeletal system included weakness 6 (5.7%), joints pain 3 (2.8%), and leg cramps 2 (1.8%); from auditory system included hearing loss 6 (5.7%) and from dermatological disorder included rashes in 3 (2.8%).

Table 7: Adverse drug reactions observance DOTS versus PMDT regimen.

Regimen	No. of patients reported with ADRs/ total no. patients according to inclusion criteria	Percentage
DOTS	73/235	31.06
PMDT	12/20	60

Isoniazid presented with highest percentage of ADRs i.e. 41 (30.6%) followed by rifampicin 35 (26.1%), pyrazinamide 22 (16.4%) and other (Table 4).

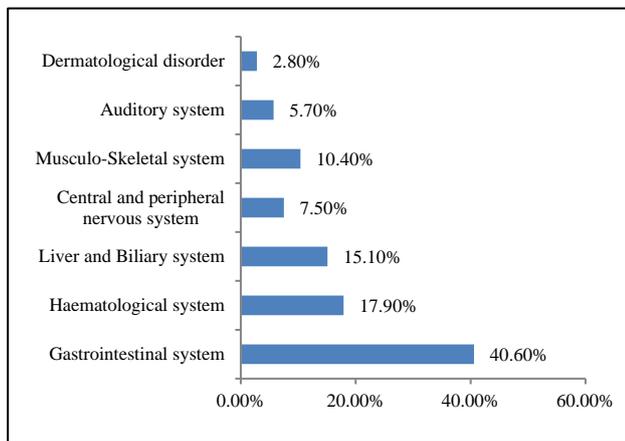


Figure 1: Details of system specific adverse drug reactions.

Majority 60 (56.6%) of ADRs were serious and 46 (43.4%) were non serious. Out of 60 serious ADRs, majority required hospitalization/prolong stay in 50 (47.2%) (Table 5).

The WHO UMC scale assessments revealed that out of 106 ADRs, 64 (60.4%) were possible, 40 (37.7%) were probable and 2 (1.9%) were certain type of ADRs. None of the ADR reported under unlikely, unclassified or unassessable category (Table 6).

As per severity assessment using Modified Hartwig and Siegel scale, out of 106 ADRs majority 86 (81.1%) were moderate grading, 13 (12.3%) were mild grading and 7 (6.6%) were severe grading (Table 7).

In present study, occurrence of ADRs was more among PMDT therapy (60%) in comparison to DOTS therapy (31.06%). Z test applied and the p value = 0.0084

(significant p value <0.05). This suggests higher ADRs in PMDT, as compared to DOTS regimen (Table 8).

DISCUSSION

Tuberculosis is hazardous health problem in developing country like India. In the present study the proportion of ADRs were more among females (46.6%) as compared to males (28.1%). Similar to present study, Ramanath et al i.e. 31.58% and Yee et al reported higher percentage of ADRs among females. Generally, females are considered to be more at risk of ADRs due to poor nutritional status, ignorance for the health and diet, smaller body size and body weight.^{8,13}

Maximum number of patients with ADRs belonged to the age group of 21-30 years in present study i.e. 23 (27.1%). This result is similar to study Chhetri et al i.e. (29.33%).⁸ This age group is highly vulnerable to ADRs, due to their high exposure to public places, substandard working environment and ignorance for diet and health.

Majority of ADRs were reported under 40 Kg of weight. This is similar to the study carried out by Kapadia et al.¹² In a developing country like India malnutrition is a major health problem which leads to poor immunity and so could be associated with adverse effects.

In present study, the most commonly affected system by ADRs was gastrointestinal system. There are few studies which report equivalent results to present study.¹³⁻¹⁶

As per one Nepal study Chhetri et al⁸, tingling at hand and feet reported as highest percentage among all ADRs. It differs from result of present study because patients advised isoniazid without supplementation of pyridoxine in that study. In present study, the recommended doses of isoniazid used with supplementation of pyridoxine as per RNTCP guideline.

As per assessment in Verma et al study, majority (68.88%) of ADRs were of mild grading and no case of severe grading was reported. It was retrospective study and ADRs associated with only first line antitubercular drugs were observed.¹⁷

According to WHO - UMC causality scale majority of reactions in present study were ‘possible’ 64 (60.4%) followed by ‘probable’ 40 (37.7%) and ‘certain’ 2 (1.9%). There are few studies which report equivalent results.^{14,15}

Modified Hartwig and Siegel scale revealed that majority of ADRs 86 (81.1%) were of moderate grading. There are few studies available which shows similar results.^{14,16}

There is significant difference between the proportions of DOTS versus PMDT regimen induced ADRs. PMDT therapy includes second line drugs with higher adverse drug effects and less potency possibly the reason for high rate of ADRs.

Limitations

Due to noncompliance and practical infeasibility, outdoor patients were omitted and only indoor patients were included in the study. The study had a narrow zone of tertiary care hospital. It should be more extensive incorporating outdoor patients and rural areas.

CONCLUSION

Antitubercular treatment is safer but early detection, management and reporting of ADRs is required to prevent it at initial stage and helps to decrease default rate and drug resistant strain.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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