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Causality Assessment of Adverse Drug Reactions in Tuberculosis Patients who are on Directly Observed Treatment Short Course Strategy in Mysore District

Mahendra Kumar BJ [1], Soumya Mathew[2], Ramesh S[3], Uma Maheswari D[4], Hymavathi R[5], Srikanth MS[6]

[1] Director PG Studies, Prof. & Head, Department of Pharmacy Practice, JDT Islam College of Pharmacy, Jamiath Hill, Kozhikode – 673012,Kerala, India.

[2] Department of Clinical Pharmacy, SAC College of Pharmacy, BG Nagara, Karnataka, India.

[3,4,5,6] Department of Clinical Pharmacy, SAC College of Pharmacy, BG Nagara, Karnataka, India.

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ABSTRACT

Tuberculosis (TB) is one of the foremost public health problems, curable disease if diagnosed and treated properly with antituberculosis drugs. In addition to disease related complications there are serious adverse drug reactions due to Anti-tuberculosis therapy**.** The present study was carried out to monitor, document and reporting of Adverse Drug Reactions (ADRs) in Tuberculosis patients who are on Directly Observed Treatment Short course (DOTS) strategy and to assess their causality by using Naranjo and WHO algorithms. This was a prospective observational and active surveillance study conducted over a period of 9 months. Each reported Adverse Drug Reaction was documented and assessed for its causality as per standard algorithms. A total of 128 Adverse Drug Reactions were identified out of which the prevalence of Adverse Drug Reactions 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 Adverse Drug Reactions, 128 (100%) Adverse Drug Reactions were probable and based on WHO probability assessment scale 119 (92.97%) were possible where as 9 (7.03%) were probable. The study concluded that Directly Observed Treatment Short course therapy is safer but regular monitoring of Adverse Drug Reactions should be adopted.

Keywords: Tuberculosis, Antituberculosis drugs, Directly Observed Treatment Short course, adverse drug reactions.

INTRODUCTION

Tuberculosis (TB) is a contagious infection caused by an airborne bacterium, *Mycobacterium tuberculosis*.[1] Early days physicians referred Tuberculosis as *Phthisis*, derived from a Greek term for wasting, because it's clinical presentation consisting of weight loss, cough, fever and hemoptysis.[2]

Based on the WHO surveillance and survey 9.27 million TB cases were found in 2007 (139 per 100000 population). Asia (South East Asia and Western Pacific regions) accounts for 55% of global cases, African region for 31% and other regions include America, Europe and Eastern Mediterranean accounts for a small fraction of global cases. India ranks first in the estimated number of Tuberculosis cases and approximately 1962 cases per 11, 69,016 population at the rate of 168 cases per 10,00,000 population.[3] To control and reduce TB and its social burden Government of India in collaboration with WHO and World Bank launched a programme called RNTCP (Revised National Tuberculosis Control Programme).[4]

A higher incidence of ADRs was noticed with antituberculosis drugs. Long duration of treatment for Tuberculosis with drugs like Isoniazid, Pyrazinamide, Rifampin, Ethambutol and Streptomycin causes adverse drug reactions like hepatotoxicity, visual disturbance, arthralgia, headache and skin rashes, mostly tend to occur in the first three months of therapy.[5]

According to WHO, Adverse Drug Reaction (ADR) is defined as 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. Patients with multiple drug therapy are prone to develop an adverse drug reaction either due to alteration of drug effect through an interaction or by synergistic effect. Multiple or intercurrent disease, age, gender, race and genetics are also responsible for increased risk of developing an ADR.[6]

Identification of an ADR can be useful for the prevention, early detection and management of ADRs. In ADR monitoring programs causality assessment of ADRs is an important step. Naranjo's algorithm and the WHO Probability scales are commonly used to carry out the assessment of causality of the ADRs. Hence, there is a need to study the safety of patients on DOTS through the monitoring of ADRs.[5] 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] Pharmacists have an ethical obligation to notify whenever ADRs are suspected and encouraged to report which inturn helps to minimize ADRs.[8, 9]

A large number of patients are exposed to anti-TB drugs at primary health centres (PHCs) in RNTCP/DOTS. In this context, this study was undertaken with the objectives to

Address for Correspondence:

Dr. BJ Mahendra Kumar, Director for PG Studies, Prof. & Head, Department of Pharmacy Practice, JDT Islam College of Pharmacy, Jamiath Hill, Kozhikode – 673012, Kerala, India.

E-mail: bjmahendrakumar2003@yahoo.co.in

monitor, document and reporting the ADRs in TB patients who are on DOTS strategy and to assess its causality by using Naranjo and WHO algorithms.

MATERIAL AND METHODS

Study design: This was a prospective observational and active surveillance study.

Study site: The study was conducted in the RNTCP/DOTS centers of Mysore district.

Subjects: All the patients from the study sites who were on DOTS for TB treatment/ newly started on DOTS were enrolled into the study after taking their consent.

Study period: Study duration was 9 months.

Materials used: TB treatment card, patient consent form, patient data collection form, suspected ADR notification form, Naranjo and WHO algorithms.

Study procedure:

The study protocol was approved from the Institutional Human Ethical Committee of Adichunchanagiri Institute of Medical Sciences (AIMS), BG Nagara before conducting the study. A written informed consent was taken from each patient before enrolling them in to the study. Patient information was collected from both the TB treatment card and also by interviewing the patient. The TB treatment card provides information regarding patient demographic details like age, weight, type of TB, HIV status, date of initiation of therapy, phase of treatment, date of completion of therapy and history of previous Anti-TB therapy. All the required information received from the patient was documented in the suitably designed patient data collection form. Information about the ADR experienced by the patient can be obtained by interviewing the patient. If ADRs were detected, they were brought to the notice of the medical officer for further evaluation. Details regarding the suspected drug, date of initiation of suspected drug, 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 officer. All the suspected ADRs were assessed for their causality by using the WHO ADR probability scale and Naranjo's algorithm.[11, 12] The documented data was subjected for suitable statistical analysis.

RESULTS

During the study period 175 patients were diagnosed with Tuberculosis who was on routine treatment protocol. Among 175 patients, 53 (30.28%) developed ADRs. Total number of adverse drug reactions detected in this was 128.

The prevalence of ADRs was more in the age group of 41-50 years (41.38%) followed by 33.33% at the age group of 61 years and above, and 30.77%, 28.57% at the age groups of 21-30, 11-20 years of age respectively. Female patients had higher prevalence of ADRs 31.58% when compared to males 29.66%. The prevalence of ADRs was higher in underweight patients 34.17% followed by overweight 33.33% and normal weight 21.15%. The former smokers were more prevalent to ADRs 32.9% than non-smoker 31.71% and current smoker 11.76%. The prevalence of ADRs was found high with non-alcoholics 32% followed by past or former alcoholics 30%. Current tobacco users were more prevalent to ADRs 100% than former tobacco users 32.26% and non-tobacco users 28.88%.

The prevalence of ADRs was found high with pulmonary TB 31.75% and followed with extra pulmonary TB 26.53%. The patients who were on intensive phase were more prevalent to ADRs 46.53% than who were on continuous phase 8.11%. The prevalence of ADRs was found high with Category II 42.11% followed by Category I 27%. The prevalence of ADRs was found more with patients having co morbid conditions 75% followed by the patients not having any co morbid conditions. Out of these 75% of patients, 85.71% had DM as shown in Table No. 01.

ADR's affected the Skin and appendages were high 27 (21.09%) followed by Gastro intestinal system 15 (11.73%), Musculo skeletal system 15 (11.72%), Central and peripheral nervous system 10 (7.81%), Vision 4 (3.12%). The most commonly identified adverse drug reactions affecting Skin were pruritis 27 (21.09%) followed by rashes 08 (06.25%), Gastro intestinal system were nausea 15 (11.73%), followed by vomiting 11 (08.59%), heart burn 02 (1.56%), diarrhoea, abdominal pain, flatulence 01 (0.78%**),** Musculo skeletal system were arthralgia and myalgia 15 (11.72%), Central and peripheral nervous system disorders were dizziness, headache 10 (7.81%) followed by neuropathy 08 (06.25%) and Vision was blurred vision 04 (03.12%) as shown in Table No. 02.

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%) were categorised as probable. The assessment done by using WHO scale revealed that out of 128 ADR's 119 (92.97%) were possible and 09 (7.03%) were probable as shown in Table No. 03. Out of 128 ADRs 59 (46.1%) were recovered, 43 (33.6%) were improved and 26 (20.31%) were continuing. Symptomatic treatment was not given to 80 (62.5%) ADRs and given to 48 (37.5%) ADRs. Out of 53 patients, for 52 (98.1%) patients therapy was continued with the suspected drug and for 1 (1.9%) patient the suspected drug was discontinued.

DISCUSSION

In our study the prevalence of ADRs is comparatively more in the age group of 41-50 years. These observations are contrast to the study conducted by Gholami K *et al.*[10] The prevalence of

Table1: Details on prevalence of ADRs in Tuberculosis patients

Characteristics	No. of patients n=175(%)	No. of patients with ADR n=53(%)	Prevalence %
Age (in years)			
01-10	004 (02.30)	000 (00.00)	00.00
11-20	014 (08.00)	004 (07.54)	28.57
21-30	039 (22.30)	012 (22.64)	30.77
31-40	053 (30.30)	015 (28.30)	28.30
41-50	029 (16.60)	012 (22.64)	41.38
51-60	027 (15.40)	007 (13.21)	25.93
61 & above	009 (05.10)	003 (05.67)	33.33
Gender			
Male	118 (67.40)	035 (66.04)	29.66
Female	057 (32.60)	018 (33.96)	31.58
BMI (kg/m2)			
Underweight	120 (68.60)	041(77.36)	34.17
Normal	052 (29.70)	011 (20.75)	21.15
Overweight	003 (01.70)	001 (01.89)	33.33
Smoking status			
Former smoker	076 (43.40)	025 (47.17)	32.90
Current smoker	017 (09.70)	002 (03.77)	11.76
Non-smoker	082 (46.90)	026 (49.06)	31.71
Alcohol status			
Former Alcoholic	070 (40.00)	021 (39.62)	30.00
Current Alcoholic	005 (02.90)	000(00.00)	00.00
Non-Alcoholic	100 (57.10)	032 (60.38)	32.00
Tobacco use status			
Former Tobacco user	031 (17.70)	010 (18.87)	32.26
Current Tobacco user	002 (01.10)	002 (03.77)	100.0
Non-Tobacco user	142 (81.10)	041 (77.36)	28.88
Diagnosis			
Pulmonary TB	126 (72.00)	040 (75.47)	31.75
Extra Pulmonary TB	049 (28.00)	013 (24.53)	26.53
Phase of Anti-TB treatment			
Intensive Phase	101 (57.70)	047 (88.68)	46.53
Continuous phase	074 (42.30)	006 (11.32)	08.11
Category of treatment of TB			
Cat I	137 (78.30)	037 (69.81)	27.00
Cat II	038 (21.70)	016 (30.19)	42.11
Any other co morbid conditions and medications used			
Absent	167 (95.40)	047 (88.68)	28.14
Present	008 (04.60)	006 (11.32)	75.00
DM	007 (04.00)	006 (11.32)	85.71
DM, HTN, AST	001 (00.50)	000 (00.00)	00.00

Table 2: Details of ADRs based on organ system wise

Organ systems affected	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(06.29)
Nausea	15(11.73)	15(08.57)
Diarrhoea	01(00.78)	01(00.57)
Abdominal pain	01(00.78)	01(00.57)
Heart burn	02(01.56)	02(01.14)
Flatulence	01(00.78)	01(00.57)
Skin and appendages disorders	35(27.34)	29(16.57)
Pruritis	27(21.09)	27(15.43)
Rash	08(06.25)	08(04.57)
Musculoskeletal system disorders	30(23.44)	22 (12.57)
Arthralgia	15(11.72)	15(08.57)
Myalgia	15(11.72)	15(08.57)
Central and peripheral nervous system disorders	28(21.88)	23(13.14)
Dizziness	10(07.81)	10(05.71)
Headache	10(07.81)	10(05.71)
Neuropathy	08(06.25)	08(04.57)
Vision disorders	04(03.12)	04(02.29)
Blurred vision	04(03.12)	04(02.29)

Table 3: Details on causality of ADRs based on Naranjo and WHO assessment scales

Causality assessment of ADRs	No. of ADRs (n=128)(%)
Naranjo algorithm	
Probable	128(100.00)
Possible	000(000.00)
WHO probability scale	
Probable	009(007.03)
Possible	119(092.97)

ADRs observed in female patients (31.58%) was higher compared to male patients (29.66%), which was similar to the studies conducted by Gholami K *et al*[10] and Kishore PV *et al.*[11] In underweight patients the prevalence of ADRs was observed more (34.17%) because of their low socio-economic status, poor nutrition and lack of awareness about the medication.

The prevalence of ADRs was more in non-alcoholics (32%) which were similar to the study conducted by Chhetri AK *et al*.[12] But the prevalence of ADRs observed was more in former smokers (32.9%) and former tobacco users (32.26%) which were contrast with the study conducted by Chhetri AK *et al*.[12]

Patients with the history of previous Anti-TB treatment, who were on intensive phase and Category II treatment, had the

higher prevalence of ADRs 40%, 46.53% and 42.11% respectively. The patients who had the history of previous Anti-TB treatment will be treated with Category II which includes Isoniazid, Rifampicin, Pyrazinamide, Etahmbutol and Streptomycin. The prevalence of ADRs increases with poly pharmacy.[6]

The prevalence of ADRs was found to be higher in patients with only TB than in patients with co morbidities like Diabetes Mellitus, Hypertension and Asthma. Among these co morbid conditions, diabetes was found to be major. The lack of immune power in diabetic patients might be the reason for TB and prevalence of ADRs.

Organ system classes involved in ADRs:

Our study observed that skin and appendages was the most common organ system affected. It was noted that pruritis was found to be the major ADR 27 (21.09%). These findings were contrast to one of the study conducted at Imam tertiary care hospital, Iran.[10]

Gastrointestinal system was the second most organ system commonly affected. Observed ADRs included nausea which is major 15 (11.73%) followed by vomiting, heartburn, diarrhoea, abdominal pain and flatulence. Gastrointestinal system was found to be a common system affected due to ATT (Anti Tubercular Therapy) in the study conducted by Tak DK *et al* and Ghosh S *et al*.[5, 13]

The occurrence of ADRs like arthralgia and myalgia were found to be 15 (11.72%). The study findings of arthralgia was related to that of the study conducted by Chhetri AK *et al*[12] and Sharma TN *et al*.[14]

Dizziness was observed in 10 (7.81%) of the patients enrolled in the study. Similar results were found in the study conducted by Chhetri AK *et al*.[12] Headache and neuropathy were also observed in our study which was related to the study conducted by Gholami K *et al*.[10]

Blurred vision was observed in 4 (3.12%) patients which is similar to the study conducted by Gholami K *et al*[10] and Kishore PV *et al*.[11]

Assessment of ADRs:

Naranjo algorithm is used widely for carrying out causality assessment of ADRs. It is based on the points given for each of ten questions that comprise the algorithm. After obtaining the points they were categorised under Definite ≥ 9, Probable 5-8, Possible 1-4, Unlikely $\leqslant 0$. Majority of the patients showed probable under this scale, which is similar to the studies conducted by Gholami K *et al*[10] and Kishore PV *et al*.[11]

In the WHO assessment scale certain, possible, probable, unclassifiable, unlikely and unclassified were considered for assessing ADRs. 119 (92.97%) were possible and 09 (7.03%) were probable based on WHO scale which is similar to the study conducted by Tak DK *et.al*.[5]

The main aim of DOTS strategy is to combat TB. Even though ADRs occur, there is no change in the treatment. In our study anti TB drugs were stopped only in one patient due to the severity of ADR and symptomatic treatment was given to few patients to subside the ADRs. Majority of the ADRs did not affect the therapy with the anti-TB drugs as they recovered without giving any symptomatic treatment.

Limitation

- Lack of laboratory investigations like plasma or tissue drug concentrations, liver function tests and haematological tests were not done.

Future directions

- Proper education should be given to the patients about the ADRs caused due to ATT which may reduce defaulter rates and would enhance medication adherence.
- Monitoring of ADRs induced by ATT in all RNTCP/DOTS centres should be explored.
- Implementation of spontaneous reporting system in the RNTCP/DOTS programme can be useful in identification of new ADRs to ATT.

CONCLUSION

This study showed that the prevalence of ADRs was high with first line anti-TB drugs (DOTS therapy). The adverse drug reactions increases remarkably as number of drugs rises. This study concluded that there is a need of a system for proper monitoring of ADRs caused by anti-TB drugs. Counselling of patients by a health care professional for timely prevention of ADRs is necessary as the treatment adherence can be achieved.

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