**Research Article**

# A Study of Anti-Tubercular Drug Induced Adverse Reactions in Patients Attending Pulmonary Medicine Department of a Tertiary Care Teaching Hospital

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**ABSTRACT**

Tuberculosis (TB) has been one of the common diseases in our society for the past 40 years. India accounts for one-fifth of the global TB cases. Each year nearly 2 million people in India develop TB. 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. The main objective of the study is to collect the demographic details of the patients receiving anti tubercular therapy, identify the incidence & pattern of ADRs caused by anti tubercular drugs and to assess the causality & severity of the reported ADRs. All patients attending to Pulmonary Medicine department at I.M.S. & SUM Hospital, a tertiary care teaching hospital in eastern India, receiving Anti-TB drugs for at least eight months were included in study. These patients were monitored for ADRs during OPDs & hospital stay. Any Adverse effects observed were recorded in 'Adverse Drug Event Reporting Form' prepared by the CDSCO, Govt. of India & the demographic details in study proforma prepared by the study team. The data were evaluated for patient demography, types of TB, incidence of ADRs, onset and outcome of the ADRs. ADRs were also assessed for their causality and severity by using world Health Organization –Uppsala monitoring centre (WHO-UMC) criteria& Hartwig's scale. Of the 91 TB patients, majority were males (71%). Gastritis was the most common ADR (36.8%) and multiple drug therapy was the major predisposing factor. On evaluation of the causality of ADRs, majority of them were found to be 'possible' by WHO-UMC & Naronjo's causality assessment scale. The severity assessment of ADRs showed that 51% reactions were moderate and 49% were of the 'mild' nature.

**Keywords:** Adverse Drug Reaction, Tuberculosis, WHO-UMC.

## INTRODUCTION

Tuberculosis (TB) has been one of the common diseases in human communities during the past 40 years. TB is a bacterial infection caused by organisms belonging to the *Mycobacterium tuberculosis* complex.[1] India accounts for one-fifth of the global TB cases. Annually around 330,000 Indians die out to TB. The World Health Organization (WHO) declared TB as a global emergency in 1993.[2] Southeast Asia dominates the worldwide distribution of notified cases (36% of the total cases). The global rate of tuberculosis is growing at approximately 1.1% per year.[3] India ranks first in the estimated number of tuberculosis cases & approximates to 1761 (thousands) cases per 10, 49,549 population at the rate of 168 cases per 1, 00, 000 population.[3] In order to intensify the efforts to control TB, the Government of India gradually replaced NTP (National Tuberculosis Programme) by the DOTS strategy/programme in 1993, now known as the Revised National Tuberculosis Programme (RNTCP). The objective of this revised strategy is to achieve a cure rate of 85% for infections and seriously ill patients through intermittent (three days a week) supervised short course chemotherapy or the directly observed treatment, short course (DOTS).[4] Antitubercular drugs, just like other drugs used in clinical practice, are not free from ADRs. The added problem is that combinations of drugs are always used for prolonged periods of time and therefore, it is likely that the adverse reactions of one drug may be potentiated by the companion drugs used. Moreover, the Adverse Drug Reactions (ADRs) to the drugs used is one of the major reasons for the patient default for treatment. A general knowledge of the various ADRs and their management is essential for the effective management of TB.[5] All antitubercular drugs can cause adverse drug reactions[6] and may result in ADRs involving almost all systems in the body, including the gastrointestinal tract, liver, skin, nervous system, otovestibular apparatus and eyes.[7] The WHO defines ADR as 'A response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.[8,9] Naranjo's Algorithm[10] and the WHO probability Scales[9] are commonly used to carry out the assessment of the causality of the ADRs. Similarly, the Hartwig *et al* Scale[11] is a commonly used scale for identifying the severity of ADRs. Morbidity & mortality is partly due to disease-related complications & partly due to serious adverse drug reactions (ADRs) induced by Anti-TB drugs. So, it has become the need of the hour to monitor for ADRs & increase awareness of ADRs.

Thus the present study was undertaken;

1. To collect the demographic details of the patients receiving antitubercular therapy.
2. To identify the incidence & pattern of ADRs caused by the anti tubercular drugs.
3. To assess the causality & severity of the reported ADRs.

## PATIENTS AND METHODS

A prospective, observational clinical study was carried out for eight months (March - October 2012) in pulmonary medicine department in collaboration with Dept. of pharmacology of our hospital. All the patients of tuberculosis were enrolled after taking their informed consent & monitored for ADRs. Patient profile was maintained to identify the patient demography, type of treatment, disease classification, date of start & completion of treatment, record of follow-up, types of TB, 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. 91 cases were studied for ADR monitoring during the study period and causality was assessed using world Health Organization –Uppsala monitoring centre (WHO-UMC) & Naronjo's causality assessment scale. Severity was assessed by Hartwig's questionnaire.

## OBSERVATION AND RESULTS

A total number of 91 patients who were on DOTS therapy were included in our study, of which 65 patients i.e around 71% were male & 26(28.6%) were female. 48 patients were under 36 years of age (52.7%) followed by 32 resides in the age of 36 – 65 (35.2%). Rest were in more than 65 years age group (12.1%) (Table 1). The patients of TB in the study were divided according to their type of TB, like pulmonary (88/96.7%) & extra pulmonary (3/3.3%).

**Table 1:** Demographic Profile of patients receiving Anti tubercular drugs (n=91)

| Parameters | | Number | Percentage (%) |
|---|---|---|---|
| Gender | Male | 65 | 71 |
| | Female | 26 | 29 |
| Age group (in years) | Under 36 | 48 | 52.7 |
| | 36-65 | 32 | 35.2 |
| | More than 65 | 11 | 12 |
| Type of TB | Pulmonary | 88 | 96.7 |
| | Extra pulmonary | 3 | 3.3 |
| Type of DOTS | Category I | 40 | 44 |
| | Category II | 51 | 56 |

Out of these 91 patients only 15 patients developed 19 ADRs of various types (Table 2). Among the 19 reported ADRs, most were observed in males (15/78.9%) & remaining (4/21.1%) were females. Out of 19 ADRs, 10 (57%) were from patients on Category II of the DOTS therapy, followed by 9 (43%) from Category I. The overall incidence of ADRs was 20.87%. ADRs in this study were categorized according to the systems affected like gastrointestinal system, skin, nervous system & other systems like vestibular, muscle etc. Majority of ADRs were

related to gastrointestinal system (8 cases) followed by central nervous system (4 cases), other systems (5 numbers) & 2 cases of skin eruption (Figure 1). Gastritis was the most common ADR (36.8%) followed by skin reaction & peripheral neuropathy (10.52%). In 87.1% of the cases, the suspected drug was continued in spite of the ADR, without any complications.

Two (10.52%) of the ADRs occurred on the first day of the treatment. 6 ADRs (36.8%) occurred within a week of treatment, 5 (28.57%) in the second week, 3 (16.28%) in the third week & 1(5.26%) in each following weeks of the initiation of anti tubercular therapy. Out of the 19 cases, dechallenge of the suspected drug was done in 1 (5.26%) case and definite improvement was observed. On evaluation of the causality of ADRs, a majority of them were found to be 'possible' by both WHO-UMC and Naranjo's scales. 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 51% reactions were moderate and 49% were of the 'mild' nature as per the Hartwig *et al* scale.

## DISCUSSION

Out of 91 patients enrolled in the study, 15 patients developed 19 ADRs (20.87%). The highest numbers of ADRs [15 (78.94%)] were observed in males which is in contrast to the study by Yee & Shakya et al[12] who considered female gender as a risk factor for the occurrence of ADRs due to anti-TB drugs. But in the study, by D.K.Tak et al[13], males developed more ADRs, which could be due to majority of males included in the study. In our study, 48 patients were under 36 years of age (52%) followed by 32 resides in age of 36-65 (36%) & eleven were in more than 65 years age group (12%). This result is in contrast to the study by Yee et al[12] where age over 60 years was associated with increased incidence of ADRs due to anti TB drugs. A study conducted by Daphne *et al*[13] showed that ADRs due to anti tubercular drugs occurred in patients above the age of 60 years. But in the present Study, majority of ADRs were observed in patients below 60 years of age. In our study 9 (47%) ADRs were observed in age group of less than 36 years & 36-65 years. 10 ADRs (57%) were from patients on Category II of the DOTS therapy, followed by 9 (43%) from Category I. Two (10.52%) of the ADRs occurred on the first day of the treatment. 6 ADRs (36.8%) occurred within a week of treatment, 5 (28.57%) in the second week, 3 (16.28%) in the third week & 1(5.26%) in each following weeks of the initiation of antitubercular therapy.

Out of the 19 cases, dechallenge of the suspected drug was done in 1 (5.26%) case & definite improvement was observed. The highest reported ADR was gastritis (36.8 %) which is in accordance to the study by Dhingra *et al*[15], where it was around 53%. Peripheral neuropathy, characterized by a tingling and burning sensation in the hands, feet & skin reaction (Figure-2) was 2nd most common ADRs observed in our study population, whose

occurrence was comparable to that found in the study conducted by Dhingra et al,[15] where it was around 17%. On evaluation of the causality of ADRs, a majority of them were found to be 'possible' by both WHO-UMC and Naranjo's scales. 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 51% reactions were moderate and 49% were of the 'mild' nature as per the Hartwig et al scale.

**Table 2:** Incidence of ADRs in different systems (n=19)

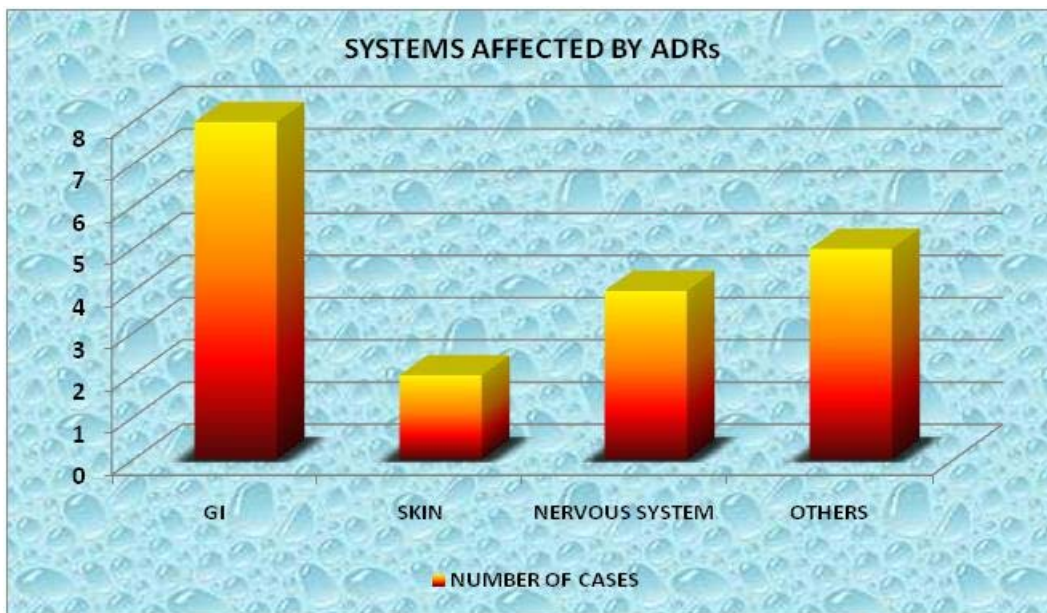| Systems affected by ADR | Type of ADRs | Number | Percentage (%) |
|---|---|---|---|
| Gastrointestinal | Hepatitis | 1 | 5.26 |
| | Gastritis | 6 | 36.8 |
| | Anorexia | 1 | 5.26 |
| Skin | Skin reactions | 2 | 10.52 |
| Nervous system | Peripheral neuropathy | 2 | 10.52 |
| | Dizziness | 1 | 5.26 |
| | Psychosis | 1 | 5.26 |
| Others | Ototoxicity | 1 | 5.26 |
| | Vertigo | 1 | 5.26 |
| | Weakness | 2 | 10.52 |
| | Arthralgia | 1 | 5.26 |



**Figure 1:** ADRs in different systems



**Figure 2:** Anti tubercular drug induced acneform eruptions.

**Limitations and future implications of the study**

Use of anti-tubercular drug use is safe, but regular monitoring is required to prevent ADRs at the initial stage. Majority of the patients seem to have mistaken the symptoms of ADR to be due to the disease being treated. The study concluded that there is need of a system for proper monitoring for ADRs due to anti tubercular drugs. Small sample size, confined to a single hospital only, a short Period of follow up & inability to rechallenge are the other limitations. Yet the study clearly provides the baseline data for comparing similar studies at the level of state, country and the world. It also provides the information regarding the management of the adverse drug reactions and their outcome thus making the drug therapy safer and more rational. This study has added up

in the direction of strengthening the activity of pharmacovigilance in this part of the country.

## CONCLUSION

Anti tubercular drugs, just like other drugs used in clinical practice, are not free from ADRs. They may cause significant reactions both in severity & quantity leading to abstinence from therapy, prolonged hospital stay &even death. In our study, the number of ADRs was high in males. Gastritis was the most common ADR and multiple drug therapy being the major predisposing factor. Majority of the ADRs reported in this study were categorized as 'possible'& mild to moderate severity. In majority of the cases, the suspected drug was continued in spite of the ADRs, without any complications. Counselling of patients for timely prevention, detection and management of ADRs was also highly suggestive.

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