CRITICAL ASSESSMENT OF ADVERSE DRUG REACTIONS TO ANTITUBERCULAR DRUGS IN A GOVERNMENT TEACHING HOSPITAL

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ABSTRACT

Background: Antitubercular drugs just like other drugs used in clinical practice are not free from ADRs (Adverse drug reactions). The added problem is that combination of drugs are used for prolonged periods of time. Moreover the ADRs to drugs used is one of the major reasons for patient default, hence leading to emergence of resistant organisms. Identification of the ADR profile of drugs in a hospital setup can be useful for the prevention, early detection and management of ADRs.

Objectives:

1) To study the demographic profile of patients receiving Antitubercular therapy.
2) To identify the pattern of ADRs caused by Antitubercular drugs in T.B. patients.
3) To assess causality and severity of the reported ADRs.

Methodology: A prospective observational study conducted for six months at PKTB Hospital of MMCRI, Mysore. All the T.B. patients admitted from November 2011 till April 2012 were included as per the study criteria and were monitored for ADRs. The data were evaluated for patient demography, type of T.B., type of DOTS treatment, type of ADRs and Organ site/system affected. ADRs were then subjected to causality assessment as per Narango algorithm and severity assessment as per Hartwig and Siegel method.

Statistical methods applied are Frequencies, Cross tabs and Chi-Square test.

Results: Out of 133 patients, majority were males (87.2%), belonged to the age group of 31-40 years (31.6%), of body weight 36-45 kgs (43.6%), were from rural areas (61.7%) and were illiterates (72.9%). Pulmonary type of T.B. was more common (95.5%), majority had smear status positive (73.7%) and were of category 1 type of DOTS (57.9%). The most common organ system involved was G.I.T. both alone and in association with C.N.S. The most common type of ADR was nausea, both as an individual ADR, as well as in association with other ADRs like gastritis, vomiting etc.

On evaluation of the causality of ADRs, majority were found to be possible (64.7%). The severity assessment showed that most of the patients ADRs were of mild level-1 (81.2%).

Conclusion: Regular ADR monitoring is required to reduce morbidity and development of multiple drug resistance among patients with ADRs and also to improve patient compliance.

Key words: Adverse drug reactions, Antitubercular drugs, Causality assessment, Severity assessment.

INTRODUCTION

Tuberculosis is a disease of great antiquity caused by Mycobacterium tuberculae. This disease has accounted for more human suffering, loss of earnings and failure of social and economic development compared to any other disease. Today, Tuberculosis has become the most important communicable disease in the world, with over 8 million cases of pulmonary tuberculosis occurring each year, 95% of which are in developing countries. India, a country with over 1.21 billion people, accounts for 20% of the global incidence of tuberculosis, thus sharing the highest burden of TB among the countries in the world.

Since the beginning of the twentieth century, India has been in the forefront of TB research and control. The National Tuberculosis Control Program was launched in 1962, but it suffered from inadequate funding, weaknesses in management, irregular drug supply and multiple treatment regimens. Then the
Revised National Tuberculosis Control Program was piloted in 1993 and was based on DOTS. DOTS which was the internationally recommended strategy for TB control promoted diagnosis by sputum smear microscopy, direct observation of treatment, standardized regimens, recording and reporting of notified cases and treatment outcomes and over and above all political commitment.

The standard anti-TB short course chemotherapy is the key component of the DOTS strategy. This requires continually taking drug combinations of different antitubercular drugs every alternative day for a prolonged period of time. It is currently used in majority of the countries with higher TB burden. These drugs, in addition to their role in destroying and inhibiting Mycobacterium tuberculae, also cause different kinds of adverse drug reactions involving almost all systems in the body including the gastrointestinal system, liver, skin, nervous system, otovestibular apparatus and eyes. ADR of one drug may be potentiated by a companion drug. These Adverse drug reactions are the major cause of noncompliance to antitubercular treatment.

In India, Tuberculosis is a disease which is strongly associated with poverty and deprivation. TB patients encounter innumerable constraints in getting proper treatment and adhering to it. Many studies have shown various reasons for default such as inconvenience of clinic timings resulting in loss of wages, cost of travel to the clinic, lack of provision for continuity of treatment in case of a family emergency resulting in a missed visit to the clinic, poor management of adverse events and toxicity.

Therefore despite the availability of effective chemotherapy, TB is still a major health problem in most countries. This can be attributed to poor patient compliance, to primary multidrug resistance and to interruption partly due to adverse drug reactions.

Adverse drug reactions not only contribute to noncompliance to therapy but, may also lead to stoppage of treatment due to their severity. This further causes development of resistant strains requiring second line therapy of drugs with higher cost and more serious adverse drug reactions. The nature of adverse drug reactions is also influenced by various factors like genetic, environmental, diet, disease pattern, nutritional status, paucity of data because of limited ADR monitoring centers and use of modern drugs along with traditional remedies.

Adverse drug reactions also contribute to excessive healthcare cost through increased patient morbidity and mortality which is of great concern to the general population, the pharmaceutical industry, the regulatory authorities and the medical profession.

**Hence we are carrying out this study with the following objectives:**

a. To collect demographic details of the patients with adverse drug reactions to antitubercular drugs.

b. To identify the incidence and pattern of ADRs caused by antitubercular drugs in TB patients.

c. To assess causality and severity of the reported ADRs.

**METHODOLOGY**

This study was carried out in PKTB hospital attached to Mysore Medical College and Research Institute, Mysore. It is a tertiary care hospital of a government medical college which is the oldest college in Karnataka State, inaugurated in the year 1924.

A total of 133 patients satisfying the inclusion criteria were included in the study. The potential study subjects were interrogated for history in the local dialect and detailed information pertaining to the disease was elicited. A medical specialist carried out a thorough clinical examination for both pulmonary and extra pulmonary TB cases. Special clinical features like Cough (more than 3 weeks) Yellow expectoration / Haemoptysis Evening rise in temperature Night sweats Loss of appetite Loss of weight H/o contact with TB patients Other physical findings were noted.

The subjects underwent the following laboratory investigations to confirm the diagnosis, to be
included in the study.

- X-ray chest (P/A view)
- Sputum for AFB smears
- Sputum for AFB culture and sensitivity tests (in selected subjects)
- Blood for TC, DC & ESR.
- Mantoux test
- FNAC / Biopsy (in selected subjects)

The patients were followed up on a weekly basis during the period of treatment

**Inclusion criteria :-**

1. The patients diagnosed with pulmonary and extra pulmonary TB based on various clinical features and laboratory investigations.
2. Patients admitted to the wards or visiting OPD of PKTB Hospital diagnosed with TB.
3. Patients of either sex with TB
4. Patients who gave informed consent to participate in the study.

**Exclusion criteria :-**

1. Patients unable to respond to verbal questions.
2. Patients below 12 years of age
3. Pregnant and lactating females
4. Patients with liver / kidney disease
5. Patients with Diabetes / Hypertension.

**Study Design**

This was a prospective observational study to monitor adverse drug reactions to anti-TB drugs in both inpatients and outpatients at PKTB hospital of MMCRI, which is a tertiary care teaching hospital.

**Study Duration :-**

The study was carried out over a duration of 6 months (from November 1st, 2011 till April 30th, 2012).

**Study Schedule :-**

The patients were enrolled after oral informed consent as per inclusion and exclusion criteria. After enrolment into the study, the current medical history and diagnosis was noted during the first visit and then at weekly intervals follow up was done during treatment. Any new complaints were recorded at each follow up. Adverse effects, if any were recorded in detail at each visit.

**Ethics Committee Approval :-**

The Institutional Ethics Committee approval was taken before the study was carried out.

The patients were grouped into demographic characteristics to evaluate adverse drug reactions.

- Age
- Sex
- Body weight
- Marital status
- Residence
- Literacy
- Occupation

**Status Of TB**

- Type of tuberculosis
- Smear status
- Type of DOTS treatment
- Type of ADRs
- Past History Kochs
- Organ site/system involved.

- Frequency of episodes of ADRs induced by anti-TB drugs were studied.
- All suspected ADRs were also evaluated for their causality using Naranjo algorithm.
- Severity assessment was done using the modified Hartwig and Siegel scale.

**Tool used :-**

A self developed patient profile form was used for the study. The data obtained from the filled patient profile forms were entered in the Microsoft excel spread sheet and analyzed.

Statistical methods applied were frequencies, cross tabs and chi-square test. All statistical calculations were done through SPSS for windows (version 16)
**Table 1: Demographic Parameters of patients on ATT affected with ADRs.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Frequency</th>
<th>Percentage</th>
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<td><strong>Age (in years)</strong></td>
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<td>&lt;20 yrs</td>
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<tr>
<td>21-30 yrs</td>
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<td>51-60 yrs</td>
<td>22</td>
<td>16.5</td>
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<tr>
<td>&gt;60 yrs</td>
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<td>6.8</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Female</td>
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<tr>
<td><strong>Body weight (kgs)</strong></td>
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<tr>
<td>&lt;35</td>
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<td>15.8</td>
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<td>56-65</td>
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<td><strong>Educational Status</strong></td>
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<td>Literate</td>
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<td><strong>Marital Status</strong></td>
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<td>97.7</td>
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<td>61.7</td>
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<tr>
<td>Urban</td>
<td>51</td>
<td>38.3</td>
</tr>
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</table>
RESULTS

A total of 133 patients who developed ADRs to antitubercular drugs were enrolled for the study. Out of 1148 patients on ATT only 133 patients developed adverse drug reactions that is an incidence rate of 11.4%. Among them a majority of them were males (87.2%), nearly one third were in the age group of 31-40 years (31.6%), most of them were of body weight 36-45 kgs (43.6%). A large proportion of them were from rural areas (61.7%). 97.7% of them were married and 72.9% of patients with ADRs were illiterate.

Pulmonary type of TB was more common (95.5%) and majority of the cases had smear status positive (73.7%). 57.9% of the pts with ADRs were of category 1 type of DOTS.

Only 8.3% of the cases were reactive to HIV

Association of ADRs :-

The most common type of ADR was nausea, both as an individual ADR (22) as well as in association with other ADRs like Gastritis (11), Vomiting (10), Weakness (3), Dizziness (1)

Other Common Associations of ADRs were

Gastritis with vomiting (2), Gastritis with weakness (2), Pruritis with gastritis (1), Dizziness with weakness (1), Vomiting with dizziness (1), Vomiting with peripheral neuropathy (1), Vertigo with gastritis (1), Diarrhoea with vomiting (1), Least association was seen with seizure

Organ systems affected by ADRs :-

The most common organ system involved was Gastrointestinal both alone (76) and in association with the Central Nervous System (18).

Management of the ADRs :-

Two patients developed seizures and they were referred to K.R. Hospital for further evaluation to rule out Tubercular meningitis, Tuberculoma or INH induced seizure and were not available for follow up.

One case of Hepatotoxicity was detected, first all drugs were withheld and they were reintroduced one by one and it was found to be a case of INH induced hepatotoxicity (dechallenge followed by rechallenge).

Two cases of streptomycin hearing loss were detected and were treated by withdrawing the drug.

There was a rare case of generalized itching induced by Paraamino salicylic acid, where the drug was withdrawn. A case of pyrazinamide induced arthritis was also detected and treated symptomatically. In cases of minor ADRs like GIT symptoms, symptomatic treatment was given and the treatment was continued.

Causality assessment :-

As per Narango algorithm 64.7% ADRs were possible, 2.3%. ADRs were unlikely and 33.1% were probable.

Severity assessment

81.2% of the cases were mild (level-1)
13.5% were mild (level 2)
3.8% were moderate (level 3)
And 1.5% were moderate (level 4)

DISCUSSION

Tuberculosis is a serious public health problem in India and one among the major killer diseases. The emergence of multidrug resistant TB and the spread of HIV / AIDS are contributing to the worsening impact of the disease. Major adverse reactions to antitubercular drugs can cause significant morbidity and compromise treatment regimens for tuberculosis.

These events may result in substantial additional costs because of added outpatient visits, investigations and in more serious instances hospitalization. Alternative agents may have greater problems with toxicity and treatment is often prolonged, with attendant challenges to ensure compliance. As a result, the risk of treatment failure and relapse are higher.

Hence there is a need to study the safety of patients
on antitubercular drugs by monitoring ADRs in a hospital set up. Identification of the ADR profile of drugs can provide valuable information for the prescribers and policy makers in implementing appropriate measures to prevent the occurrence of similar ADRs.

In our study, the incidence of ADRs was 11.4%. Two studies from Russia reported a variable incidence of 72.8% (Chukanow et al) and 16.9% (Mishin et al). Another study from U.K reported an incidence of 5.1% (Ormerod and Horsfield 1996). A study from Nepal showed an incidence of 12.27% (Kishore PV et al). A study from Manipal, India (Tak DK et al) showed an incidence of 17.02%. There is a wide variation in the incidence of ADRs depending on the place and time of the study.

In our study, males have a higher incidence of ADRs 87.2%. Some studies have shown females to have a higher incidence of ADRs (eg : Yee et al, Kishore PV et al). They opine that it might be because they pass through life stages like pregnancy, menarche etc which modify drug response. However some studies like Tak DK et al showed higher incidence in males (70%). This may be because predisposing factors like smoking and alcoholism are more common in males.

The incidence is higher in rural areas (61.7%) compared to urban areas. This is probably because our study was conducted in a government hospital and it caters to the needs of the poorer sections. Also exposure to unhygienic conditions, exposure to animal dander, malnutrition etc may also contribute to higher incidence. On similar grounds we can attribute to the higher incidence among the illiterate (72.9%).

A recent WHO guidelines on treatment of TB mentions extra pulmonary TB to be accountable for 20-25% of the reported cases. It is more frequent in children and persons with HIV. In our study only 4.5% were extra pulmonary TB comparable with Tak DK et al (4%) and Daphne et al (9%)%. This may be because only severe cases of extra pulmonary TB were referred to PKTB hospital and children (in whom it is more common) were not included in the study.

Here 59.9% of the cases had TB for the first time and 36.1% for the second time. In 57.1% of the cases GIT was involved. This is probably because GIT symptoms develop due to multidrug therapy all taken by the oral route. This is comparable with studies like Dhingra et al (53%), Kishore et al (53%).

Carrying out the causality assessment using standard methods is one of the best ways to establish the causal relationship between a drug and its effect. The Naranjo algorithm is widely used in carrying out the causality assessment of ADRs. It is based on the scores calculated on the basis of points given for each of ten questions that comprises the algorithm. On a scale of 13, if the score is greater than 9, then the adverse reaction is categorized as definitely caused by the particular drug. A score of (5-8) is categorized as probably caused by the drug and a score of (1-4) is categorized as possibly caused by the drug. 64.7% of the cases had a possible relation with the drug.

In order to take proper initiatives towards the management of ADRs, it is necessary to study the severity of ADRs. Hartwig's scale is widely used for this purpose. This scale categorises the reported adverse drug reactions into different levels as mild, moderate or severe. This is helpful in deciding whether hospitalization is required or not. Here majority of the cases were mild (81.2%).

CONCLUSION

TB is a disease of poverty with several known social determinants (eg : Malnutrition, tobacco smoking, alcoholism etc) that are not adequately addressed by the DOTS strategy.

All patients undergoing treatment for the disease should be closely assessed at least monthly to identify and address potential adverse reactions.
The reactions may range from inconsequential to severe and may be caused by medications other than those prescribed for TB drugs.

So, to have the highest likelihood of success, chemotherapy must be provided within a clinical and social framework based on an individual patient's needs.

REFERENCES


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