Original Article

Adverse drug reaction monitoring through active surveillance of antitubercular therapy in an urban tertiary care center

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ABSTRACT

Background and Objectives: 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. 1) We aim to study the demographic profile of patients receiving Antitubercular therapy. 2) To identify the pattern and incidence of ADRs in the intensive phase Antitubercular therapy following DOTS strategy. **Materials and Methods:** A descriptive longitudinal study conducted for twelve months at tertiary care hospital in Eastern India. All the adult T.B. patients attending the outpatient department from January 2015 till December 2015 were included as per the study criteria and were monitored for ADRs. The data were evaluated for patient demography, type of DOTS treatment, type of ADRs and Organ site/system affected. ADRs were then subjected to severity assessment as per Hartwig scale.Statistical analysis was done using statistical software Graf Pad Prism version 4.03 for Windows. **Results:** Out of 296 patients, majority were males (59.79%), belonged to the age group of 20-30years(53.37%). Out of 296 patients 196 patients developed 312 detected ADRS mostly reported in the 5th week of DOTS therapy. In 11(5.61%) cases drugs were withdrawn, 21(10.71%) cases drugs were reduced and remaining 164 (83.67%) cases drugs were continued in original dose. Among them 164 cases received symptomatic treatment. The most common organ system involved was G.I.T. The most common type of ADR was nausea and vomiting (23.07%). On evaluation of severity assessment showed that most of the patients ADRs were of mild level-1(79.39%). **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 reaction, antitubercular drugs, directly observed treatment short-course therapy, tuberculosis

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INTRODUCTION

Tuberculosis (TB) is a contagious and airborne infectious disease. It is a disease of poverty affecting mostly young adults in their most productive years. According to the WHO 2015 report, the vast majority of TB deaths are in the developing world including India and other Asian countries. About one-third of the world's population is infected with TB bacteria.[1]

The TB death rate has fallen by 35% since 1990, and the number of deaths is also declining. Globally, the percentage of people successfully treated reached the highest level at 86% in 2008. Since 1995, 41 million people have been successfully treated and up to 6 million lives saved through directly observed treatment short-course (DOTS) and the stop TB strategy. 5.8 million TB cases were notified through DOTS programs in 2009.

Antitubercular drugs (ATDs), just like other drugs have some adverse effects. As these drugs are used in combination for prolonged periods for the treatment of TB, adverse effect of one drug may be potentiated by the companion drugs. The adverse effects involve almost all systems in the body, namely, the gastrointestinal tract, liver, skin, nervous system, eyes, etc., Studies from different parts of world suggest that more than 5% of the patients on antitubercular treatment develop adverse drug reactions (ADRs). Some of the ADRs can be even fatal.[2-4]

However, no such data regarding prevalence is available in the present set-up. Hence, in this study, we have recorded the adverse effect profile of the commonly used ATDs through active surveillance in a hospital set up and compared it with the available data. We have also assessed the severity of the ADRs using the Hartwig *et al*. scale[5] for better ADR monitoring.

Objectives

This study was undertaken to find out the incidence of ADR in the intensive phase of antitubercular therapy following DOTS strategy and to compare the result with standard data of this incidence.

MATERIALS AND METHODS

This was descriptive longitudinal study spanning between January 1st and December 31st, 2015. The study was carried out in the Pharmacology Department and Chest Medicine Department of a tertiary care hospital in Eastern India. The study was begun after obtaining approval from the Institutional Ethical Committee. The study included adult patients attending the chest medicine outpatient department with TB without preexisting liver disease, ophthalmopathy, or neuropathy. Patients who did not consent to participate were excluded. Patients previously exposed to ATDs, i.e., those in Category II were also excluded.

After inclusion each of the patients was monitored for 2 months for the appearance of ADRs while being administered the following ATDs: Isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E). The schedule for visits were:

- Second visit on the 1st week of therapy
- Third visit on the 3rd week of therapy
- Fourth visit on the 5th week of therapy
- Fifth visit on the 7th week of therapy.

ADRs (if any) have been identified or detected by interviewing these patients on their visits, about the appearance of certain clinical features pertaining to the ADRs. Any intervention following the appearance of ADRs was also recorded. The ADR profile and adopted intervention measures (if any) for all the study subjects have been preserved by using case sheets for future reference.

The results obtained from this study have been analyzed statistically and compared with the results obtained from other similar studies to see if there is any statistically significant deviation. Statistical analysis was done using statistical software GraphPad Prism version 4.03 for Windows (Graphpad Software Inc., San Diego, CA, USA). All the ADRs have been assessed for their severity using the Hartwig *et al*. scale [Table 1].[5]

The Hartwig *et al*. scale[5] categorizes the reported ADRs into different levels as mild, moderate, or severe.

RESULTS

A total of 296 TB patients who attended the chest medicine outpatient department receive ATDs (DOTS therapy) were included in the study as per the stated inclusion and exclusion criteria. The demographic details of the patients selected for the study are given in Table 2.

Of total 296 patients, 196 patients developed 312 ADRs, the incidence rate being 66.21%. Among the 312 ADRs most occurred in the age group between 20 and 30 years (53.37%). Results showed that of the 196 patients with ADRs 102 (52.04%) patients suffering from ADRs were male. The different types of ADRs detected are denoted with their incidence in Table 3.

Of the total number of 312 detected ADRs 104 (33.33%) were reported in the 3rd visit or 5th week of DOTS therapy, followed by 94 (30.12%), 91 (29.16%), and 32 (10.25%) ADRs in the 1st, 3rd, and 7th week of DOTS therapy, respectively.

Of the 196 patients who developed ADRs, in 11 cases (5.61%) the drugs were withdrawn (ATD was stopped). The dosage of the drugs was reduced in 21 cases (10.71%). In the remaining 164 cases (83.67%), drug was continued in original dose in spite of ADRs. Among them 164 cases (128 or 65.3%) received

symptomatic treatment and the other 36 cases (21.95%) received no treatment.

Of the 196 patients who reported with different types of ADRs, 137 patients (69.89%) recovered without any complication before the end of the study. In the remaining 59 cases, ADR continued beyond 2 months. The different types of ADRs were assessed for their severity as per the Hartwig *et al*. scale.[5] In most of the cases, the ADR belonged to Level 1 235 cases (79.39%). The severity assessment of the ADRs is given in a tabular form in Table 4.

DISCUSSION

Among the 296 TB patients who were selected for this study, after fulfilling the specific inclusion and exclusion criteria, 196 (66.21%) patients were detected with at least one adverse reaction. However, as several patients presented with multiple adverse reactions the total number of ADRs detected in the study was 312.

Table 1: The Hartwig *et al.* scale for adverse drug reactions[5]

Level	Criteria
Mild (Level 1)	The ADR requires no change in the treatment with the suspected drug.
Mild (Level 2)	The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay
Moderate (Level 3)	The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required with no increase in length of stay
Moderate (Level 4)	Any level 3 ADR that increases the length of stay by at least one day or The ADR is the reason for admission
Severe (Level 5)	Any level 4 ADR that requires intensive medical care
Severe (Level 6)	The ADR causing permanent harm to the patient
Severe (Level 7)	The ADR either directly or indirectly leading to the death of the patient

ADR: Adverse drug reaction

Table 2: The demographic details of the patients receiving directly observed treatment short-course (*n*=296)

Parameters	*n* (%)
Gender	
Male	177 (59.79)
Female	119 (40.2)
Age group (in years)	
20-30	158 (53.37)
31-40	82 (27.7)
41-50	29 (9.79)
51-60	27 (9.12)
Type of DOTS	
Category I	227 (76.68)
Category III	69 (23.31)

DOTS: Directly observed treatment short-course

The high incidence of ADR affected patients in this study (66.21%) indicates that more such studies should be undertaken in this region to corroborate the results and to see whether patients residing in this area are more susceptible for developing ATD induced ADRs.

The incidence of ADRs in this study (66.21%) is almost 4 times high when compared with the result obtained by Tak *et al*. (17.02%)[6], and almost double as compared to that found in the study carried out by Marra *et al*.,[7] (30%). Other studies conducted by Kim *et al*.,[8] Chhetri *et al*.,[9] and Gholami *et al*.[10] showed the ADR incidence to be 52.6%, 54.75%, and 53.01%, respectively. The incidence of ADR due to ATDs in this study (66.21%) is almost similar to the result (66%) obtained by Zierski and Bek[11] The ADR incidence in this study is less when compared to the ADR incidence (80%) as detected by Koju *et al*.[12] These variations in results could be attributed to the varying number of study subjects in these studies.

Table 3: List of adverse drug reactions detected as per WHO adverse drug reactions terminology and the implicated drugs (total number of adverse drug reactions=312)

System affected by ADR	Types of ADR	*n* (%)
Gastrointestinal system disorders	Nausea and vomiting	72 (23.07)
	Hepatitis	43 (13.78)
	Anorexia	25 (8.01)
	Diarrhea	11 (3.52)
Skin and appendages disorders	Skin rashes	17 (5.44)
	Urticaria	21 (6.73)
Respiratory system disorders	Cough	
	With hemoptysis	19 (6.08)
	Cough without hemoptysis	7 (2.24)
Central and peripheral nervous system disorders	Tingling sensation in peripheral nerves	12 (3.84)
	Dizziness	32 (10.25)
General disorders	Weakness and fatigue	27 (8.65)
	Fever	18 (5.76)
	Insomnia	1 (0.32)
	Hypersomnolence	7 (2.24)

N.B.: In many instances a single patient has been detected with multiple ADRs. Hence, the total number of ADRs recorded is more than the number of affected patients. ADRs: Adverse drug reactions

Table 4: Evaluation of the severity of adverse drug reactions; using Hartwig *et al.* scale[5]

Level of severity	*n* (%), *n*=296
Level 1	235 (79.39)
Level 2	18 (6.08)
Level 3	32 (9.09)
Level 4	11 (3.71)
Level 5	0
Level 6	0
Level 7	0
Level 7	0

Most of the literature say that the female gender is more prone to develop ADRs induced by ATDs.[7,13,14] However, in the present study, marginally higher male patients reported ADRs with ATDs (52.04%). This result is consistent with the findings of the studies conducted by Tak *et al*.[6] and Chhetri *et al*.[9] As most of the patients in this study were males (59.79%) so probably males reported more ADRs.

This study revealed that most of the ADRs were seen in patients aged 20–30. Gholami *et al*.[10] have shown that ages over sixty increase the risk of ADRs due to ATD. This is probably because most of the study patients belonged to a younger age group. Chhetri *et al*.[9] have; however, shown higher incidence of ADRs due to ATD in the young.

In this study, the system mostly affected by ADRs is the gastrointestinal system (48.38%). This is comparable to that found in the study conducted by another study.[15] In the same study,[15] the second most common system to be affected was skin (22.1%). In this study, skin related incidence of ADRs was 12.17%. Zierski and Bek[11] have shown drug withdrawal or alternation in 1.8% patients. In this study, drug was withdrawn in 5.6% patients and the dose was reduced in 10.7% patients. The drugs were continued in original dose in spite of ADRs in 83.67% patients as compared to 87.1% patients in the study conducted by Tak *et al*.[6]

In this study, 69.89% patients recovered from ADR without any complication before the end of 2 months from the inception of DOTS. In this study, most of the ADRs were of Level 1 or mild category 79.39% and only 3.71% needed hospital admission (Level 4b). Chhetri *et al*.[9] reported 93.33% of Level 1 severity while in the study conducted by Gholami *et al*.[10] 38.2% of the ADRs had severity Level 1.

CONCLUSION

The strategy for TB control is a step toward achieving the TB-related Millennium development goals in terms of reducing the prevalence of TB by 50% by 2015.[16] It can be concluded that the study showed that DOTS therapy is safe, but more comprehensive monitoring of the patients undergoing antitubercular therapy is required to prevent or reduce the incidence of such adverse effects, at the initial stages.

Limitation

This study had a few limitations. One of the major limitations was that only outpatient department patients were recruited. As the study was conducted entirely on OPD patients, their cooperation and compliance played a major role. Because of the lack of resources, biochemical tests could not be performed on the patients and the study is entirely based on clinical findings.

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Conflicts of interest

There are no conflicts of interest.

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