Original Research Article

Adverse Reactions Due to Directly Observed Treatment Short Course Therapy: An Indian Prospective Study

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Abstract

Introduction: Tuberculosis (TB) causes enormous social and economic disruption and hampers nation's development. DOTS strategy under RNTCP is one of the largest public health programs found to be beneficial against TB. Adverse drug reactions lead to decrease in patient compliance and adherence. Good patient adherence to the treatment regimen is the foundation stone to effective anti-tubercular therapy. Noncompliance is cited as the major problem to the control of the tuberculosis at the level of public health which finally leads to drug resistance in case of TB.

Aim and Objectives: To identify the occurrence and pattern of Adverse Drug Reactions (ADRs) associated with anti-tubercular drugs in TB patients under DOTS therapy during Intensive phase of treatment.

Materials and methods: A prospective observational study was conducted in 2 randomly selected DOTS centers of Jalandhar. A total of 102 patients of categories I and II who were registered in third quarter of 2014 were selected for study. The follow up period was during the intensive phase of DOTS regimen. All patients on ATT were followed up at the end of 1 week, 1 month and after the completion of intensive phase or if/ when self reporting was done due to adverse drug reactions. Detection and monitoring of adverse drug reaction was done by interviewing patients, consulting with physicians about the patient's clinical problems, reviewing laboratory test and medical records. The data so collected was entered and analyzed using SPSS 21 software.

Results: The Incidence of adverse drug reaction was observed in 20.4% i.e. 21 out of 102 patients. Total number of adverse reactions developed in 21 patients were 31, with most common being GIT

system (38.7%), followed by skin problems (29%). History of alcoholism, associated co-morbidities, pulmonary TB and DOTS treatment Category II were found to be significantly associated with occurrence of ADRs.

Conclusion: The present study highlighted the importance of developing strategies to ameliorate ADRs both to improve the quality of patient care and to control TB safely. In addition, a proper educational counseling may promote more ADR reporting by patients. These strategies may improve the patient adherence to treatment and therapeutic outcome.

Key words

DOTS, RNTCP, Tuberculosis, Adverse Drug Reactions.

Introduction

Tuberculosis (TB) puts enormous social and economic disruption and hampers nation's development [1, 2]. India accounts for one-fifth of the global TB burden, with 1.8 million developing the disease each year and of them about 800,000 are infectious. Nearly 0.4 million are dying due to TB annually which translates to two deaths every three minutes [3]. The disease is most prevalent in the age group of 15 to 54 years [4, 5] which is the highly economically productive period of an individual's life with important consequences for the household when the individual falls sick with TB [6].

Directly Observed Treatment Short course (DOTS) strategy is one of the largest public health programmes found to be beneficial against TB. This strategy has been successful in reducing death rates and increasing cure rates in India [7, 8]. Anti-tubercular treatment (ATT) exhibit greater level of efficacy with a satisfactory degree of toxicity; however combination treatment, especially during the intensive phase of therapy may produce severe adverse events [9]. There may be considerable morbidity, even mortality, particularly with drug-induced hepatitis. These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations [10]. Alternative agents may have greater problems with toxicity, and are often less effective, so that treatment must be prolonged.

Adverse drug reactions (ADRs) lead to decrease in patient compliance and adherence [7]. Good patient adherence to the treatment regimen is the foundation stone to effective anti-tubercular therapy. Noncompliance is cited as the major problem to the control of the tuberculosis at the level of public health and finally which leads to the drug resistance in case of TB [8]. So close monitoring of adverse drug reactions and its effective management is required. Pharmacovigilance activities can help in obtaining real information of safety and efficacy of medicine when they are being used in the population [11].

This study therefore aimed to explore the occurrence and pattern of ADRs associated with ATT drugs in TB patients during Intensive phase of treatment among patients being treated with a DOTS strategy.

Aim and objectives

To identify the occurrence and pattern of ADRs associated with anti-tubercular drugs in TB patients under DOTS therapy during Intensive phase of treatment.

Material and methods

Study design: Prospective observational study.

Study population: All the patients of categories I and II who were registered in third quarter of 2014 in 2 randomly selected DOTS centre of Jalandhar were selected for study. The follow up period was during the intensive phase of DOTS Regimen.

Sample Size: Total number of patients registered during the study period were 107, out of which 102 patients could be contacted (1 patient died of natural causes, 3 moved out of community and 1 did not give consent for study).

Study method: Detailed information pertaining to socio-demographic data was recorded in case record form. Before anti-TB therapy, participants received several laboratory examinations, including CBC, Hb, urine routine and microscopy, liver and renal function tests & hepatitis B surface antigen (HBsAg) test.

All patients on ATT were followed up at the end of 1 week, 1month and after the completion of intensive phase or if/ when self reporting was done due to adverse drug reactions. At the end of two months, blood and urine routine test as well as liver and renal function tests were done again.

Detection and monitoring of adverse drug reaction was done by interviewing patients, consulting with physicians about the patient's clinical problems, reviewing laboratory tests and medical records.

Adverse Drug Reactions Definitions

ADR was defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product [12]. Serious ADRs were defined as any untoward medical occurrence that at any dose results in death requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening [12].

- Liver dysfunction was accepted as an increase in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin greater than two times the upper limit of normal (ULN) or higher than ULN in two continuous tests conducted in a two week interval, not considering the symptoms.
- Hepatotoxicity was defined as an increase in ALT or AST that was greater than three times of ULN, or in total bilirubin greater than two times of ULN [13].
- Hyperuricemia was defined as an increase in uric acid levels of more than 8 mg/dl.
- Anemia was defined as haemoglobin (Hgb) concentration, 11 g/dl in male and, 10 g/dl in female patients without a history of anemia or more than 1 g/dl drop in Hgb concentration after anti-TB treatment.
- Neutropenia and thrombocytopenia were recognized as a drop in absolute neutrophil count and platelet count equal to or less than 1500 cells/mm3 and less than 150000 cell/mm^3 respectively.
- Except liver dysfunction, hematologic system disorders and renal impairment were determined based on laboratory examination, other ADRs including allergic reactions, arthralgia and nervous system disorders were determined based on symptoms.
- Nervous system disorders included auditory nerve damage, optic nerve damage, peripheral nervous damage and central nervous system damage.
- ''-Others'' referred to those ADRs which could not be classified to above types, such as interstitial pneumonia, hyperthyroidism, lipsotrichia and so on.

Statistical analysis: The data so collected was entered in Microsoft Office Excel Sheet and analyzed using SPSS software version 21. P value of less than 0.05 was taken as level of significance.

Results

A total of 83 patients were registered under category 1 while remaining 19 were under category 2 (**Table - 1**). Males constitute about

two third (66/102) of the study population. Out of total 102 cases, 60.8% were of pulmonary TB while rest 39.2% were of Extra – pulmonary TB (**Table - 2**). The Incidence of adverse drug reaction was observed as 20.4% i.e. 21 out of 102 patients (**Table - 3**). Total number of adverse reactions developed in 21 patients were 31, with most common being GI system related (38.7%), followed by skin problems (29%), Liver dysfunction (9.7%) hepatotoxicity (6.5%) and haematological diathesis (3.2%). One case each was noted of visual and hearing problems, hyperurecemia and joint pain (**Table - 4**). Symptomatic management was done for most of the patients while ATT was withheld in 2 cases with hepatotoxicity. History of Alcoholism, associated co-morbidities, pulmonary TB and DOTS treatment Category II were found to be significantly associated with incidence of ADRs ($p< 0.05$; **Table - 5**).

Table – 1: Distribution based on category of treatment.

Category	No. of patients	%
I	83	81.4%
II	19	18.6%
Total	102	100.0%

Table – 2: Distribution based on type of TB.

Type of TB	No. of patients	%
Pulmonary	62	60.8%
Extra-pulmonary	38	37.2%
Total	102	100.0%

Table – 3: Distribution based on development of ADR.

Development of ADR	No. of patients	%
Yes	21	20.6%
No	81	79.4%
Total	102	100.0%

Table – 4: Distribution based on type of ADR.

Type of ADRs	No. of patients	%	% (total)
GI problem	12	38.7%	11.8%
Skin problems	9	29.0%	8.8%
Liver dysfunction	3	9.7%	2.9%
Hepatotoxicity	2	6.5%	2.0%
Visual problems	1	3.2%	1.0%
Hearing problems	1	3.2%	1.0%
Hyperurecemia	1	3.2%	1.0%
Hematological	1	3.2%	1.0%
Joint pain	1	3.2%	1.0%
Total	31	100.0%	30.4%

Discussion

In the present study, the incidence of ADRs associated with anti-tubercular drugs in TB patients under DOTS, was observed as 20.4%. Tak, et al. [14] conducted a study on "Safety evaluation of anti-tubercular therapy under revised national tuberculosis control program in India" in which the incidence of ADRs was found to be 17.02%. Xiaozhen, et al. [15] in their study reported an incidence of ADRs as 15% while in a study by Athira et al. [16], out of 511 patients studied, 93 patients (18.20%) developed adverse drug reactions. In a similar study by Gillani, et al. [8], out of 653 patients, 103 (15.8%) patients had an experience of adverse drug reactions.

Most common adverse reaction observed were GI related (38.7%), followed by skin problems, Liver dysfunction and hepatotoxicity. Most of the gastritis occurred within the first week of therapy. The most serious ADR was hepatitis. Only 2 patients developed increased enzyme level (ALT) greater than 3 times of the base line. Increasing plasma uric acid was observed in 1 patient, due to pyrazinamide. They experienced severe joint pain and after discontinuing pyrazinamide, uric acid returned to normal range (2.1-8.5 mg/dl) in 10 days. The only ADR

suspected to be induced by ethambutol was vision abnormality such as blurred vision and burning eyes observed in only one patient. One patient each developed hearing problem & visual problem.

Table – 5: Association of various factors with development of ADR.

Variables	Development of ADR		Total	p- value
	Yes	No		
Alcoholism	15 (24.6%)	46 (75.4%)	61	< **0.01**
Co-morbidities	19 (44.2%)	24 (55.8%)	43	< **0.01**
Pulmonary TB	14 (22.6%)	48 (77.4%)	62	< **0.05**
Category II	9 (47.4%)	10 (52.6%)	19	< **0.05**

A study conducted by Sainul Abideen P, et al. [11] reveals that, GI system, liver and biliary system is the most frequent organ system affected by ADRs. Multiple drug therapy was noticed to be a major pre-disposing factor for developing GI problem. Itching was experienced by majority of the patients. The drugs, which are responsible for itching and rash may be, pyrazinamide, rifampicin, and isoniazid. The drug which is responsible for the joint pain may be pyrazinamide and peripheral neuropathy was by isoniazid. In a study by Athira, et al. [16], majority of adverse drug reactions were GI problem (38.09%), followed by skin reaction (30.48%) then hepatotoxicity (14.28%). Lv Xiaozhen, et al. [15] observed the incidence (count) of ADR based on affected organ as: liver dysfunction 6.34% (273), gastrointestinal disorders 3.74% (161), arthralgia 2.51% (108), allergic reactions 2.35% (101), neurological system disorders 2.04% (88), renal impairment 0.07% (3) and others 0.05% (2). Gillani, et al. [8] observed that majority of the cases of adverse drug reactions were skin related, present in 51 (7.8%) patients followed by hepatotoxicity in 17 (2.6%) patients, then gastrointestinal reactions in 16 (2.5%) patients.

History of Alcoholism, associated co-morbidities, pulmonary TB and DOTS treatment Category II were found to be significantly associated with incidence of ADRs. In a study by Athira, et al. [16], among 93 patients with ADRs, 70 patients (75.26%) were from category 1 and 23 patients (24.73%) were from category II. Among 93 patients with ADRs, majority of patients (20%) were in the age group of 50-70 years. The mean age was found to be 44.92 (± 17.22 years). They also observed more occurrences of adverse drug reactions in pulmonary tuberculosis (20.56%) than extra pulmonary tuberculosis (15.28%). Among pulmonary tuberculosis patients, patients with sputum positive (54%) developed more number of adverse drug reactions. Gillani et al. [8] observed that in type of tuberculosis, majority is pulmonary tuberculosis (84.1%). In their study only 12.1% patients suffered from extra-pulmonary tuberculosis and other 3.8% suffered from both pulmonary and extra pulmonary tuberculosis. Other researchers also reported similar findings [17, 18].

Athira, et al. [16] observed that most common ADR developed in alcoholics was hepatitis 12 (12.90%). They also observed a significant association between addiction and co-morbidities with development of ADRs. Similar findings were also observed by other authors Lv Xiaozhen, et al. [15] and Gillani, et al.[8].

The principal determinants of such adverse reactions in TB patients are the dose and time of day at which the medication is administered, as well as patient ethnicity, age and nutritional status, together with the presence of preexisting diseases or dysfunctions, such as diabetes, alcoholism, impaired liver function, impaired

kidney function, drug interaction, and HIV co-infection [13, 15-18].

Conclusion

This study showed that about 21% of TB patients who received DOTS therapy developed one or more ADRs during the intensive phase of the treatment. These side effects may steer the patient to make a judgment for stopping the medications and finally lead to the occurrence of drug resistance and an amplified healthcare cost. Given the incidence of ADRs and the size of the TB population in India, the negative impact of ADRs on anti-TB treatment would be substantial. This highlights the importance of developing strategies to ameliorate ADRs both to improve the quality of patient care and to control TB safely. In addition, a proper educational campaign approach may promote more ADR reporting by patients. These strategies may improve the patient adherence to treatment and therapeutic outcome.

References

1. World Health Organization, Research For Action: Understanding and Controlling Tuberculosis in India, World Health Organization, Geneva, Switzerland, 2000.
2. J. Broekmans, K. Caines, J. E. Paluzzi. Investing in strategies to reverse the global incidence of TB. UN Millennium Project, 2005, Earthscan, Sterling, Va, USA, 2005.
3. Central TB Division, Directorate of General Health Services Ministry of Health and Family Welfare, Nirman Bhavan, New Delhi, India.
4. P. R. Narayanan. Trends in the prevalence and incidence of tuberculosis in South India. International Journal of Tuberculosis and Lung Disease, 2001; 5(2): 142–157.
5. C. J. L. Murray. Epidemiology and demography of tuberculosis in Adult Mortality in Latin America. I. M. Timaeus, J. Chackiel, L. Ruzieka, Eds., Clarendon Press, Oxford, UK, 1996, p. 199-216.
6. Rajeswari R, Balasubramanian R, Muniyandi M, et al. Socio–Economic impact of tuberculosis on patient and family in India. Int J Tuberc Lung Dis., 1999; 3: 869–877.
7. Srinivasan R, Ramya G. Adverse drug Re-action - Causality Assessment. International J research in pharmacy and chemistry, 2011; 1: 606-12.
8. Kurniawati F, Sulaiman SAS, Gillani SW. Adverse Drug Reactions of Primary Anti-tuberculosis Drugs Among Tuberculosis Patients Treated in Chest Clinic. International J of Pharmacy and Life Sciences, 2012; 3: 1331-8.
9. Gholami K, Kamali E, Hajiabdolbagh Mi, Shalviri G. Evaluation of antituberculosis induced adverse reactions in hospitalized patients. Pharmacy Practice, 2006; 4: 134-8.
10. Bhatia ML, Jain P, Ahmad M, Moghe VV, Khan ZY. Comparison of Outcomes of Two Antitubercular Regimens in Pulmonary Tuberculosis at Tertiary Care Hospital. Medical Science, 2013; 3: 275-7.
11. Abideen SP, Chandrasekaran K, Maheswa-ran U, Vijayakumar A, Kalaiselvan V, Mishra A, et al. Implementation of Self Reporting Pharmacovigilance in Anti Tubercular Therapy Using Knowledge Based Approach. J Pharmacovigilance, 2013; 1: 101.
12. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet, 2000; 356: 1255–1259.
13. Shang P, Xia Y, Liu F, Wang X, Yuan Y, et al. Incidence, Clinical Features and Impact on Anti-Tuberculosis Treatment of Anti-Tuberculosis Drug Induced Liver Injury (ATLI) in China. PLoS ONE, 2011; 7: e21836.
14. Tak DK, Acharya LD, Gowrinath K, Rao Padma GM, Subish P. Safety Evaluation

Of Antitubercular Therapy Under Revised Na-tional Tuberculosis Control Programme In India. Journal of Clinical and Diagnostic Research, 2009; 3: 1395-401.

15. Lv Xiaozhen, et al. Adverse reactions due to directly observed treatment strategy therapy in Chinese tuberculosis patients: a prospective study. PLoS ONE, 2013; 8(6): e65037.
16. Chhetri Anupa Khatri, et al. A study of adverse drug reactions caused by first line anti-tubercular drugs used in Directly Observed Treatment, Short course (DOTS) therapy in western Nepal, Pokhara. JPMA, 2008; 58(10): 531-6.
17. Marra F., et al. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. The International Journal of Tuberculosis and Lung Disease, 2007; 11(8): 868-875.
18. Furin J., et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. The International Journal of Tuberculosis and Lung Disease, 2001; 5(7): 648-655.