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Analysis of burden and outcomes of anti-tuberculosis therapy-induced adverse drug effects at a tertiary care center

Kavita Joshi[1], Arnav Tongaonkar[2], Alhad Mulkalwar[3], Aman Goyal[4]

[1]Associate Professor, [2]Resident, [3]Intern, [4]Undergraduate Student, Department of Medicine, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India

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ABSTRACT

Background: Tuberculosis (TB), one of the most ancient diseases known to mankind, is one of the ten major causes of mortality worldwide. Combinations of antibiotics, called anti-TB therapy (ATT), are given for a period of six months or more as treatment. **Aims and Objectives:** The aim of this study was to assess the incidence of adverse drug reactions (ADRs), clinical profile, severity and causality among the admitted patients taking ATT in a tertiary care hospital. **Materials and Methods:** This was a hospital-based, prospective, observational and non-interventional cohort study undertaken in the General Medicine wards of the hospital. This study was conducted from June 2017 to December 2018. The Patients' data was recorded using a structured ADR reporting form. The baseline parameters, medical history and details of underlying diseases, clinical data, characteristics of ADRs and details of medication responsible for ADRs as well as medication for treatment of ADRs were recorded. The data was analyzed using descriptive statistics with the Statistical Packages for the Social Sciences (SPSS) version 26.0 software. **Results:** Out of the 164 patients admitted due to ADRs within the study period, 45 (27.4%) developed ADRs due to anti-TB treatment. Most ATT-related ADRs involved the liver (n = 39). The severity of ADR was found to be mild in two patients (4.4%), moderate in 28 patients (62.5%) and severe in 15 patients (33.3%). 16 patients (35.6%) completely recovered, 23 patients (51.1%) were still recovering (at the time of the analysis of the data), one patient (2.2%) did not recover and five patients (11.1%) had a fatal outcome. The presence of systemic comorbidities and polypharmacy was found to be a significant risk factor associated with ATT associated ADRs. **Conclusion:** ATT is not without its side effects. About 27.4% of the patients on ATT in our study developed ADRs, a few resulting in fatality. Educating the patients about possible ADRs associated with ATT at the time of prescription can improve patient compliance and strengthen the doctor-patient relationship. Early diagnosis and treatment of ADRs associated with ATT is paramount. This requires a better surveillance system, which India is in a dire need for.

Key words: Adverse drug reactions; Anti tuberculosis therapy; Medicine; Western India

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INTRODUCTION

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as 'A noxious, unintended, and undesirable effect that occur as a result of dose normally used in man for diagnosis, prophylaxis, and treatment of disease or modification of physiological function'. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.[1] ADRs are a major public health problem. They are considered to be a leading cause of morbidity and mortality.[2] Estimated 2.9–5% hospital admissions are due to ADRs and approximately 35% of hospitalized patients experience an ADR during their hospital stay.[3] Adverse drug events can range from mild to life-threatening reactions resulting in inconvenience or serious morbidity and mortality besides being a financial burden on the society.[4]

Address for Correspondence:
Dr. Alhad Mulkalwar, Intern, Department of Medicine, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India. **Mobile:** +91-9423523055. **E-mail:** alhad.mulkalwar@gmail.com

Tuberculosis (TB) is one of the ten major causes of mortality worldwide.[5] It is an infectious disease caused by a bacterium called *Mycobacterium tuberculosis*. It usually affects the lungs (Pulmonary TB) but can also affect other organs of the body. TB can be diagnosed by chest X-ray, culture of sputum sample and multiple other tests. All countries and age groups are affected by TB, but most cases (90%) in 2016 were in adults. Almost 65% of the cases were accounted for by eight developing countries with India contributing 27% of the 10.4 million cases recorded that year.[6,7] India also accounts for about one-fourth of the global burden of multi-drug resistant (MDR)-TB.[8]

Combinations of antibiotics – called anti-TB therapy (ATT) is given for a period of six months or more as treatment.[9] With increase in the number of medications, the chances of ADRs also increase. Adequate counseling about ADRs and early reporting of the same to physicians is essential to avoid predictable ADRs.[10] Pharmacovigilance of anti-TB treatment drugs can play an important role in identifying ADRs and providing valuable feedback to physicians.

Aims and objectives

This study aimed to assess the incidence of ADRs among the admitted patients taking ATT in a tertiary care hospital. It also analysed the clinical profile of patients with ATT associated ADRs, along with the severity, causality and preventability of these ADRs.

MATERIALS AND METHODS

This was a hospital-based, prospective, observational and non-interventional cohort study undertaken at Seth GSMC and KEMH, Mumbai, Maharashtra, India. It was conducted in the General Medicine Wards. The study spanned in the Department of Medicine from June 2017 to December 2018. The study was initiated after obtaining approval from the Departmental Review Board and the Institutional Ethics Committee (IEC/167/2017). All consenting patients, of age >21 years, either admitted in the Medical Wards of the hospital for ADR following use of ATT or those who developed ATT-induced ADRs while admitted in the medical wards for another medical condition, were included in the study. Patients with intentional or accidental poisoning, drug abuse (except alcohol), and non-compliance to the prescribed medications were excluded from the study.

The patients' data was recorded using a structured ADR reporting form. The baseline parameters were assessed to obtain relevant data on demographics, clinical condition, comorbidities, relevant laboratory data and medications used. The medical history and underlying diseases, clinical data, characteristics of ADRs and details of the medications responsible for those ADRs (suspected drug, dosage, route of administration, indication, date of beginning and stopping therapy, and concomitant drugs) as well as medications for treatment of the ADRs were obtained from the clinical notes, medication charts, clinical examination, interviews with patient or his/her relatives or caregivers or ward staff, the treatment sheets, drug administration charts, dispensing records and pill/injection count validation. All patients were followed up till discharge from the hospital or their demise. The ADRs were recorded in detail in a descriptive format. The onset, duration and progress of the symptoms was noted. Data pertaining to the adverse event was recorded - the likely causative drug/class of drug, causality (WHO-UMC scale),[11] severity (Hartwig and Siegel scale),[12] avoidability (Halla's criteria),[13] systems affected, treatment administered for the same and its outcome.

Table 1: Age and gender distribution of study participants

Variable	Number of patients
Age group of patients (in years)	
21–40	23
41–60	18
61–80	4
81–100	0
Gender distribution	
Males	24 (53.33%)
Females	21 (46.67%)

Table 2: Outcome of study participants

Outcome	Number of patients (%)
Recovered	16 (35.6)
Recovering (at the time of analysis of the data)	23 (51.1)
Not recovered	1 (2.2)
Fatal	5 (11.1)
Sequelae	0 (0)

Table 3: The distribution of organ systems involved by adverse events

Organ system affected	Number of patients
Gastrointestinal	0
Renal	0
Hematological	0
Dermatological	0
Vascular	0
Metabolic	1 (2.2%)
General	1 (2.2%)
Neurological	4 (8.9%)
Liver	39 (86.7%)

Table 4: Demographic data as well as other details of the patients admitted for ATT-induced ADR

S. No.	Age group / Sex / Weight (kg)	Comorbidities and/ or addictions	Other medications	Manifesting signs and symptoms	Duration of hospital stay	Outcome	Causality / Severity / Preventability
1	41–60 M 60	Hypertension, tobacco addiction	Antihypertensives, anti-anginals	Anorexia, YDS/ YDU	5	Recovered	Probable Moderate Not preventable
2	21–40 F 60	-	-	Nausea, vomiting, YDS/ YDU	5	Recovering	Probable Moderate Not preventable
3	41–60 F 35	Polypharmacy	-	Altered sensorium, YDS/ YDU	14	Recovering	Probable Severe Not preventable
4	21–40 M 43	Polypharmacy	-	Abdominal pain, vomiting, YDS/ YDU	15	Recovering	Probable Severe Not preventable
5	21–40 F 42	-	-	Nausea, vomiting, YDS/ YDU	20	Recovering	Probable Severe Not preventable
6	21–40 F 35	-	Anticonvulsants, steroids	Altered sensorium, YDS/ YDU	2	Fatal	Probable Severe Not preventable
7	41–60 M 52	Hypertension, alcohol and tobacco addiction	Antihypertensives, antianginals	Nausea and vomiting	4	Recovering	Probable Moderate Not preventable
8	41–60 F 45	Diabetes Mellitus, hypertension, polypharmacy	Oral hypoglycemics, antihypertensives, antianginals, herbal medication	Nausea, Anorexia, Epigastric pain, YDS/YDU	5	Recovering	Probable Moderate Not preventable
9	21–40 M 35	Tobacco addiction	-	Nausea, vomiting, YDS/ YDU	7	Fatal	Probable Severe Not preventable
10	21–40 F 38	-	-	Nausea, Anorexia	3	Recovering	Probable Moderate Not preventable
11	21–40 F 39	-	Steroids	LOC, YDS/ YDU	9	Fatal	Probable Severe Not preventable
12	41–60 F 40	Polypharmacy	Anticonvulsants, steroids	Nausea, LOC	7	Not recovered	Probable Severe Not preventable
13	41–60 F 50	Diabetes mellitus, polypharmacy	Oral hypoglycemics, antiemetics	Nausea, vomiting, YDS/ YDU	7	Recovering	Probable Severe Not preventable
14	21–40 M 60	Polypharmacy	Anticonvulsants	Nausea and vomiting	27	Recovered	Probable Moderate Not preventable
15	41–60 F 65	Diabetes mellitus, Hypertension, Ischemic Heart disease, Polypharmacy	Oral hypoglycemics, antihypertensives, antianginals, anticoagulants	Decreased appetite, nausea, vomiting, YDS/YDU	7	Recovered	Probable Moderate Not preventable
16	21–40 M 45	-	-	Abdominal pain and vomiting	5	Recovering	Probable Moderate Not preventable
17	21–40 F 50	Polypharmacy	Antiemetics	Loss of vision in both eyes	30	Recovering	Probable Severe Not preventable
18	61–80 F 60	Antihypertensives and antianginals	Hypertension	Nausea, Vomiting, Loss of Appetite, YDS/YDU	5	Recovered	Probable Moderate Not preventable
19	21–40 M 50	Polypharmacy, HIV	Antiretroviral therapy	YDS/YDU, Nausea, Vomiting	5	Recovering	Probable Moderate Not preventable

(*Contd*...)

Table 4: (*Continued*)

S. No.	Age group / Sex / Weight (kg)	Comorbidities and/ or addictions	Other medications	Manifesting signs and symptoms	Duration of hospital stay	Outcome	Causality / Severity / Preventability
20	21–40 M 35	-	-	YDS/YDU, Nausea, Vomiting	6	Recovered	Probable Moderate Not preventable
21	21–40 F 40	Polypharmacy		Anorexia, nausea, vomiting	2	Recovering	Probable Moderate Not preventable
22	41–60 M 50	-	Antiemetics	YDS/YDU, Abdominal distension, Altered Sensorium	1	Fatal	Probable Severe Not preventable
23	41–60 F 45	-	-	YDS/YDU, Altered Behaviour,LOC	1	Fatal	Probable Severe Not preventable
24	41–60 F 48	Tobacco addiction	-	Nausea, Vomiting, YDS/YDU	7	Recovering	Probable Moderate Not preventable
25	21–40 M 38	-	-	Anorexia, YDS/ YDU	8	Recovering	Probable Moderate Not preventable
26	21–40 F 35	-	-	YDS/YDU, Nausea	2	Recovering	Probable Moderate Not preventable
27	61–80 M 50	Diabetes mellitus, Ischemic heart disease, Hypertension, polypharmacy	Oral hypoglycemics, Antiemetics, antihypertensives, anticoagulants, antianginals	YDS/YDU, Altered sensorium	7	Recovering	Probable Severe Not preventable
28	21–40 F 35	Renal impairment, HIV, hypertension, polypharmacy	Antiretroviral therapy, antiemetics, antihypertensives	Nausea, deranged liver function tests	5	Recovered	Probable Mild Not preventable
29	41–60 M 40	HIV, polypharmacy, alcohol addiction	Antiretroviral therapy, Antiemetics	Nausea, Vomiting, anorexia, Icterus	9	Recovering	Probable Moderate Not preventable
30	21–40 F 45	-	-	Nausea, YDS/ YDU	3	Recovered	Probable Moderate Not preventable
31	21–40 F 35	Polypharmacy	Antiemetics	Nausea, YDS/YDU	5	Recovering	Probable Moderate Not preventable
32	21–40 F 30	Polypharmacy	Antiemetics, steroids, diuretics,	Nausea, YDS/YDU	5	Recovering	Probable Moderate Not preventable
33	21–40 M 50	Alcohol, tobacco and smoking addiction	Antiemetics	Generalised weakness, YDS/ YDU/ nausea	4	Recovered	Probable Moderate Not preventable
34	21–40 M 40	Polypharmacy	Steroids, antihypertensives, antianginals, anticoagulants	Nausea and anorexia	5	Recovered	Probable Mild Not preventable
35	21–40 M 38	Polypharmacy	Antiemetics	Nausea, Vomiting, YDS/YDU	5	Recovered	Probable Moderate Not preventable
36	61–80 M 52	-	-	Nausea, Anorexia, Epigastric pain	2	Recovered	Probable Moderate Not preventable
37	21–40 M 40	-	-	YDS/ YDU, nausea	5	Recovered	Probable Moderate Not preventable

(*Contd*...)

Table 4: (*Continued*)

S. No.	Age group / Sex / Weight (kg)	Comorbidities and/ or addictions	Other medications	Manifesting signs and symptoms	Duration of hospital stay	Outcome	Causality / Severity / Preventability
38	41–60 M 50	Polypharmacy	-	Altered sensorium, irrelevant talks	15	Recovering	Probable Severe Not preventable
39	41–60 M 40	Polypharmacy	Antiemetics	Anorexia and Nausea	2	Recovered	Probable Moderate Not preventable
40	41–60 M 54	HIV, Polypharmacy and alcohol addiction	Antiretroviral therapy	Nausea, Vomiting, YDS/YDU	5	Recovered	Probable Moderate Not preventable
41	41–60 M 60	-	-	Nausea, YDS/YDU	5	Recovered	Probable Moderate Not preventable
42	61–80 F 45	-	-	Nausea, YDS/ YDU	4	Recovering	Probable Severe Not preventable
43	21–40 M 45	Polypharmacy	Antiemetics	Altered behaviour, involuntary jerky movements	7	Recovering	Probable Severe Not preventable
44	21–40 M 35	Polypharmacy	Diuretics	Multiple, dried up scaly lesions all over the body, Polyarthralgia	20	Recovered	Probable Moderate Not preventable
45	41–60 M 60	Polypharmacy	-	Behavioural changes, decreased oral intake	10	Recovering	Probable Moderate Not preventable

Statistical analysis

The data was analyzed using descriptive statistics with the Statistical Packages for the Social Sciences (SPSS) version 26.0 software.

RESULTS

Out of the 164 patients admitted due to ADRs within the study period, 45 (27.4%) developed ADRs due to ATT (22 males and 23 females). The age and gender distribution of the subjects is given in Table 1. The mean duration of stay was 7.40 days, with a standard deviation of 6.330. The causality of all subjects (n=45) was found to be probable (WHO-UMC scale). The severity of ADR was found to be mild in two patients (4.4%), moderate in 28 patients (62.5%), and severe in 15 patients (33.3%). Five cases of ATT-induced hepatitis were fatal. The summary of the outcome in patients is given in Table 2. All ADRs due to ATT were unavoidable (n=45) as per Halla's criteria. Most ATT-related ADRs involved the liver, with hepatitis (n=39). Of these, five patients had MDR TB on Category 4 ATT, making Pyrizinamide the likely causative drug. In addition, there were three cases of cycloserine psychosis, one case of ethambutol-related optic neuritis and one case of drug-induced lupus with Isoniazid, as shown in Table 3. 29 (64.4%) of the 45 patients with ADRs had comorbidities, while 23 patients (51.11%) were on polypharmacy, making these two the most frequently associated risk factors for ADRs, as displayed in Table 4.

DISCUSSION

India has been identified as a high burden country for pulmonary TB, MDR-TB and HIV-TB. MDR-TB and extensively drug-resistant TB (XDR-TB) are becoming more and more difficult to treat now-a-days, in part due to drug resistance and the requirement of prolonged treatment with less efficacious and highly toxic drugs. ADRs associated with these drugs further complicate the picture, resulting in dropouts, which further decreases the success rate of the treatment.[14] The occurrence of ADRs in patients taking ATT may be influenced by multiple factors and may range from mild gastrointestinal disturbances to serious hepatotoxicity, ototoxicity, nephrotoxicity, peripheral neuropathy and cutaneous ADRs. The overall prevalence of ADRs with first-line drugs is estimated to vary from 8.0% to 85%.[15] These findings were consistent with the present study that had an ADR prevalence of 27.4%, with liver being the most common organ involved (86.7%). Physicians should inform patients about the possible ADRs before

commencing treatment, which might help them cope with unpleasant adverse effects and also enhance adherence to the pharmacotherapy.[16] Encouraging patient follow-up for assessment may help detect those with milder symptoms of hepatitis such as nausea and anorexia before the hepatitis becomes more severe.

It is a well-established fact that as the number of medications increase, the chances of developing ADRs also increase.[17] Polypharmacy (higher drug count) and higher comorbidity scores have been consistently reported as risk factors for ADRs, especially among geriatric patients.[18] Our study was no different; with two of the major risk factors among patients being the presence of significant comorbidities (n=29) and polypharmacy (n=23). A noteworthy point for ATT is that it is important not to overemphasize the risk of ADRs but rather to assess the benefit-risk ratio since these drugs are extremely important to treat the primary disease.

Limitations of the study

Our study was not without a few limitations. Firstly, the study evaluated patients admitted to the internal medicine wards only. Secondly, it could not be ascertained that the reason for increase in the length of stay in the hospital or the patients' death was the ADR itself and not the underlying disease, as it was difficult to assess the same. Finally, all the patients were selected from a single hospital, which may affect the external validity of our study.

CONCLUSION

Our study demonstrates the various ADRs that can occur due to ATT and further emphasizes on the importance of early detection and diagnosis of the same, as evident by the non-recovering illnesses and fatalities seen in a few patients. This requires a much better surveillance system, which India is currently in a dire need for.

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Author's Contribution:
KJ- Concept and design of the study, Interpretation of results; **AT-** Review of literature and manuscript preparation, coordination, statistical analysis, and interpretation; **AM and AG-** Statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript.

Work attributed to:
Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Acharya Donde Marg, Parel 400 012, Mumbai, India.

Orcid ID:
Dr. Kavita Joshi - https://orcid.org/0000-0002-0915-9961
Dr. Arnav Tongaonkar - https://orcid.org/0000-0003-1195-5307
Dr. Alhad Mulkalwar - https://orcid.org/0000-0001-6236-3841
Mr. Aman Goyal - https://orcid.org/0000-0001-8062-5657

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