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Adverse drug reactions to first-line antituberculosis drugs at four DOTS centers in Goa, India

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Abstract:

BACKGROUND: Major adverse drug reactions (ADRs) can cause significant morbidity and can compromise the treatment regimen. This can result in substantial additional cost due to added outpatient visits to the health facility or laboratory investigations or hospitalization in serious instances. Treatment is often prolonged with additional challenge of compliance. Hence, there is a need to monitor and manage these ADRs timely for better patient care and outcome. This study was carried out with the objective of studying the pattern of ADRs due to first-line antitubercular drugs and to carry out the causality and severity assessment of the reported ADRs.

METHODOLOGY: A prospective observational study was conducted at four DOTS centers. All tuberculosis (TB) patients registered and receiving treatment under DOTS were enrolled for the study and were followed up at regular intervals till the end of their treatment. Patients' demographic, personal, disease, investigation, and ADRs details were entered in a predesigned patient recording form. Causality assessment of all ADRs were done using Naranjo algorithm. Severity assessment was done using modified Hartwig and Siegel scale. The study was approved by the institutional ethics committee of the institute. Statistical analysis was conducted using IBM SPSS Statistics for Windows.

RESULTS: Of 186 patients, 23 patients (12.26%) developed one or more ADRs. The average number of ADRs per person was 1.43. Majority of the ADRs were reported in the 20–40 years of age group and ADRs were more likely to be among females compared to males. There was no association between type of TB, site of TB, regimen of anti-TB drugs, treatment outcomes, and ADRs. Around 84.85% and 15.15% of ADRs were classified as of mild and moderate severity, respectively, as per modified Hartwig and Siegel scale, while, as per Naranjo algorithm, 72.73% of the ADRs were classified as probable and 27.27% of ADRs as possible. No ADRs were classified as definite.

CONCLUSION: Thorough understanding of the various ADRs and their management will help in the effective treatment of TB as well as designing effective counseling methods, which will help in adherence to treatment and also to have better compliance.

Keywords:

Adverse drug reaction, DOTS, drugs, tuberculosis

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Received: 01 April 2022
Revised: 26 April 2022
Accepted: 29 April 2022
Published: 21 January 2023

Introduction

Tuberculosis (TB) treatment requires a combination of 4–5 drugs to eradicate the TB bacilli. These multidrug regimens are associated with increased incidence of adverse drug reactions (ADRs) of anti-TB drug.[1] Further, adverse effects of one drug may be enhanced by the other drugs given concomitantly, thus adding up the toxicity of drugs.[2] ADRs are the major cause of noncompliance with anti-TB drugs.[3-5] Major ADRs can cause significant morbidity and can compromise the treatment regimen. This can result in substantial additional cost due to added outpatient visits to the health facility or laboratory investigations or hospitalization in serious instances.[6] Treatment is often prolonged with additional challenge of compliance. Hence, there is a

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How to cite this article: Navelkar R, Pereira IA, Vaz FS. Adverse drug reactions to first-line antituberculosis drugs at four DOTS centers in Goa, India. Indian J Health Sci Biomed Res 2023;16:115-8.

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need to monitor and manage these ADRs timely for better patient care and outcome. This study was carried out with the objective of studying the pattern of ADRs due to the first-tine antitubercular drugs to carry out the causality and severity assessment of the reported ADRs.

Aims and objectives

1. To study the incidence and pattern of ADRs occurring during DOTS therapy
2. To assess the causality and severity of reported ADRs due to anti-TB drugs.

Methodology

This was prospective observational study was conducted at four DOTS centers, operating under Revised National TB Control Programme (RNTCP), Goa. All TB patients registered and receiving treatment under DOTS from October 2015 to September 2016 were enrolled for the study. Patients diagnosed as pulmonary or extrapulmonary TB under RNTCP and those who gave informed consent to participate in the study were included in the study. Patients on non-DOTS treatment and patients with multidrug-resistant (MDR)-TB/extensively drug-resistant TB were excluded from the study. Patients enrolled in the study were followed up at regular intervals till the end of their treatment. Patients who were lost for follow-up/defaulted, died, transferred out, or switched to MDR-TB treatment were considered till they followed up under DOTS.

Patients' demographic, personal, and disease details were entered in a predesigned patient recording form. At every follow visit, patients were interviewed for suspected ADRs and the medical records/laboratory test results were also reviewed. New complaints, if any, during each follow-up visit were recorded in detail.

Causality assessment of all ADRs was done using Naranjo algorithm.[7] ADRs were categorized as possibly, probably, or definitely due to suspected drug/s under study. They are categorized as per score calculated on a basis of points given for each of 10 questions in the algorithm. Severity assessment was done using modified Hartwig and Siegel scale.[8] In this scale, ADRs are categorized as mild, moderate, or severe based on the treatment and need for hospitalization for the management of ADRs.

The study was approved by the institutional ethics committee of the institute as well as ethics committee of the Directorate of Health Services of the state. Ethics Approval Nos: No.GMC/IEC/Dec 2015/29 Dated:29/12/2015 (Institution) and No.DHS/Sp. Cell/24-166 /ethics/2015-16/1827 Dated: 15/03/2016 (Directorate of Health Services). Statistical analysis was conducted using IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY: IBM Corp). Data were presented as frequencies. Chi-square was the test of significance used to test associations between ADRs and variables of interest. $P \leq 0.05$ was considered statistically significant.

Results

A total of 186 patients were included in this study. As far as background information was concerned, majority of the participants were males (63.97%) and majority belonged to the 20–40 years of age group (50.53%). Around 67.74% of the participants had pulmonary TB and 84.4% of the participants were newly diagnosed for TB [Table 1].

Of 186 patients, 23 patients developed one or more ADRs (12.26%). Total number of ADRs reported in the study was 33. The average number of ADRs per person was 1.43.

Majority of the ADRs were reported in the 20–40 years of age group (47.82%). As far as gender was concerned, 65.22% of the ADRs were among females compared to 34.78% among males, and this difference was statistically significant [Table 2].

In patients who reported ADRs, 78.26% of patients had pulmonary TB and 21.74% of patients had extrapulmonary TB, and 86.96% of patients were on "new" treatment regimen and 13.04% of patients were on "previously treated" treatment regimen. There was no significant association between ADRs and type of TB or type of treatment regimen [Table 2].

As far as association of ADRs and treatment outcomes were concerned, among those who reported ADRs, 34.78% of patients were declared cured, 47.83% of patients were classified as treatment completed, whereas

Table 1: Background characteristics of the study participants

Variable	Male (*n*=119), *n* (%)	Female (*n*=67), *n* (%)	Total (*n*=186), *n* (%)
Age group (years)			
0-20	16 (13.45)	12 (17.91)	28 (15.05)
20-40	61 (51.26)	33 (49.25)	94 (50.54)
40-60	35 (29.41)	17 (25.38)	52 (27.96)
>60	7 (5.88)	5 (7.46)	12 (6.45)
Site of tuberculosis			
Pulp pulmonary	86 (72.27)	40 (59.70)	126 (67.74)
Extrapulmonary	33 (27.73)	27 (40.30)	60 (32.26)
Regimen			
New case	96 (82.35)	61 (91.04)	157 (84.40)
Previously treated	23 (17.65)	6 (8.96)	29 (15.60)

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Table 2: Factors associated with adverse drug reactions among the study participants

Variable	Developed ADR (*n*=23), *n* (%)	Did not develop ADR (*n*=163), *n* (%)	Total (*n*=186), *n* (%)	χ^2 (*P*)
Age group (years)				
0-20	2 (8.69)	26 (15.95)	28 (15.05)	1.39 (0.70)
21-40	11 (47.83)	83 (50.92)	94 (50.54)	
41-60	8 (34.78)	44 (26.99)	52 (27.96)	
>60	2 (8.70)	10 (6.14)	12 (6.45)	
Gender				
Male	8 (34.78)	111 (68.10)	119 (63.98)	8.32 (0.003)
Female	15 (65.22)	52 (31.90)	67 (36.02)	
Site of tuberculosis				
Pulmonary	18 (78.26)	108 (66.26)	126 (67.74)	1.33 (0.24)
Extrapulmonary	5 (21.74)	55 (33.74)	60 (32.26)	
Regimen				
New	20 (86.96)	137 (84.05)	157 (84.41)	0.13 (0.71)
Previously treated	3 (13.04)	26 (15.95)	29 (15.59)	
Treatment outcome				
Cured	8 (34.78)	48 (29.45)	56 (30.11)	1.03 (0.79)
Treatment complete	11 (47.83)	74 (45.40)	85 (45.70)	
Defaulted	1 (4.35)	17 (10.43)	18 (9.68)	
Others	3 (13.04)	24 (14.72)	27 (14.51)	

ADRs: Adverse drug reactions

4.35% of patients defaulted, and 13% of patients had other treatment outcomes, while in patients who did not report ADRs, 29.44% of patients were cured, and 45.40% of patients were classified as treatment completed. 10.42% of patients defaulted and 14.69% had other outcomes.

Most of the ADRs (93.93%) occurred in the intensive phase, while only 6.06% of ADRs occurred in the continuation phase. Around 51.51% of ADRs occurred in the 1st week of treatment, and 81.81% of ADRs occurred within a month of treatment. Majority of ADRs were related to gastrointestinal reactions (39.39%), followed by central nervous system (CNS) reactions (21.21%), skin (15.15%), hepatobiliary (12.12%), musculoskeletal (9.09%), and respiratory system (3.03%).

Among the reported ADRs, 84.85% of the ADRs were classified as mild (Level 1 and 2) and 15.15% as moderate (Level 3 and 4) as per modified Hartwig and Siegal scale. No ADRs were classified as severe. As per Naranjo algorithm, out of 33 ADRs reported, 24 (72.73%) ADRs were classified as probable and 9 (27.27%) ADRs were classified as possible. No ADRs were classified as definite.

Discussion

A total of 186 patients were enrolled in this study; among these, 23 patients (12.36%) developed ADRs to anti-TB drugs. A study from Nepal by Kishore *et al*.[9] also showed similar incidence of 12.27%. In a study conducted by Fivy K *et al*.,[10] 15.8% of the patients experienced ADRs. In a study by Mishin *et al*.,[11] ADRs were reported in 16.9% of the patients. Another study from Manipal, India, by Tak and Acharya[12] reported an incidence of 17.02%. Thus, there is wide variation in incidence of ADRs in various studies conducted at different places which may be attributed to demographic, genetic, and nutritional status variability in different population groups.

In this study, maximum number of ADRs were observed in 20–40 years of age group (47.83%) followed by 41–60 years of age group (34.78%). A study by Chhetri *et al*.[13] also reported majority of ADRs in the 20–40 years of age group (41.33%). The possible reason may be that the major chunk (70%) of TB patients belonged to the age group of 15–54 years.[14]

Among the female patients, 22.39% developed ADRs, whereas in males, the incidence was 6.72%. A study by Singh *et al*.[15] also considered female gender as a risk factor for developing ADRs due to anti-TB drugs. Females are reported to be more at risk of developing ADRs because of their smaller body size and lesser body weight.[15] Menstruation, pregnancy, or hormonal variations during different stages of life may also add to this; our study also establishes this association between female gender and ADRs.

In pulmonary TB patients, 14.29% of patients developed ADRs, whereas in extrapulmonary TB patients, 8.33% of patients developed ADRs. In "new" treatment regimen, 12.74% of patients developed ADRs whereas in "previously treated" treatment regimen, 10.34% of patients developed ADRs.

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In our study, treatment success (cured plus treatment completed) was observed in 82.61% of patients who developed ADR and in 74.84% of patients who did not develop ADRs. The overall treatment outcome in our study was not affected by ADRs. Most of the ADRs occurred during intensive phase (93.93%) compared to continuation phase (6.06%). Other studies also showed that ADRs predominantly occur in the early months of TB treatment.[16,17] Higher proportion of ADRs in intensive phase could be due to more number of drugs in intensive phase (4–5 drugs) compared to continuous phase (2–3 drugs).

The majority of the ADRs in this study involved gastrointestinal reactions (37%) such as nausea, vomiting, anorexia, epigastric upset, followed by CNS reactions (20%) such as peripheral neuropathy and vertigo. A study by Hema *et al*.[18] reported that gastro intestinal tract was involved in 57.1% of the cases. Possible reasons for this may be high pill count (4–7 pills) in multidrug therapy to be taken by oral route. A study by Sinha *et al*.[19] in Manipur has also reported similar findings.

Among the ADRs reported in this study, 84.85% were classified as mild (Level 1 and Level 2) and 15.15% as moderate (Level 3 and Level 4) as per modified Hartwig and Siegel scale. Mild ADRs require no change in treatment. In moderate category, suspected drug dose needs to be changed or drug needs to be stopped. In a study conducted by Gonzalez Montaner *et al*.,[20] 6.5% of ADRs required change in therapeutic regimen; in our study, 15.15% of ADRs required a change in therapy.

In this study, majority (72.73%) of reported ADRs were categorized as "probable" and the remaining ones (27.27%) as "possible" as per the Naranjo algorithm. Rechallenge test to establish causative agent was not done, placebo effect also was not studied, and no laboratory investigations to determine the concentration of drug in tissues or body fluids were done. Hence, none of the reported ADRs were categorized as "definite."

Conclusion

Effective counseling before the start of therapy and during therapy will help in adherence to treatment and also to have better compliance. Thorough understanding of the various ADRs and their management will help in the effective treatment of TB. This study also determines the safety of the antitubercular drugs since the ADRs were the same as those already reported in the literature.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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