Brief Research Article

Adverse Drug Reaction Patterns of First-line Anti-tubercular Drugs among Saharia Tuberculosis Patients: An Observational Study in Particularly Vulnerable Tribal Group of Madhya Pradesh, India

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Summary

The Saharia tribe of Madhya Pradesh has a very high tuberculosis (TB) burden. However, there is no report of adverse drug reaction (ADR) available in patients receiving anti-TB chemotherapy in the community. Reporting and monitoring of ADRs among TB patients is still rare in marginalized communities. An observational prospective study was performed from November 2019 to June 2020 to assess the patterns of ADRs in 250 Saharia TB patients, who were prescribed Category-I daily DOTS (HRZE) by the physician. Both male and female participants equally experienced ADR during the treatment, but relatively more females (92.6%) than males (88.6%) reported ADR during Phase I. Out of 250 patients, 224 patients (89.6%) experienced one or more ADRs in Phase I. The central nervous system-related (75.6%) ADR was mostly reported followed by any gastrointestinal (74.4%), cardiovascular (49.2%) and any dermatological related (44.4%) ADRs. It is paramount to timely monitor and proactively manages ADRs pertaining to anti-TB drug treatment with minimal alteration in the treatment course.

Key words: Adverse drug reaction, Saharia, tuberculosis

Tuberculosis (TB) is one of the leading causes of death globally. India alone accounts for 27% of the estimated global TB burden.[1] TB is a major public health problem among Saharia – a Particularly Vulnerable Tribal Group in the central Indian State of Madhya Pradesh. Several studies have reported a very high TB burden ranging from 1270 (1991–92) to 3294 (2012–13) per 100,000 population in this community[2,3] while the recently conducted national TB prevalence survey reported the prevalence of pulmonary TB (PTB) as 316 per 100,000 in the country and 386 per 100,000 populations in Madhya Pradesh, Central India.[4] Antitubercular drugs have adverse drug reactions (ADRs) of varying severity, i.e., peripheral neuropathy (isoniazide [INH]), hepatotoxicity (INH, Rifampicin [RFP], and Pyrazinamide [PZA]), cutaneous reaction, gastrointestinal (GI) such as nausea, vomiting, and anorexia, (RFP, PZA) hepatitis and sub-clinical unconjugated hyperbilirubinemia (INH, RFP), and orange staining of body fluids (RFP).[5,6] Chances of discontinuation and loss to follow-up are higher whenever the patient experience ADRs during the course of treatment thus leading to poor and unfavorable treatment outcomes. ADR in TB patients from high burden marginalized communities is of great concern, especially in view of remote tribal locations posing challenges for access to treatment and counseling. There are hardly any studies on ADR among TB patients, especially in the context of the Indian tribal population. We, therefore, conducted an observational

Access this article online

Quick Response Code:

Website: https://journals.lww.com/IJPH

DOI: 10.4103/ijph.ijph_865_22

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Submitted: 30-Jun-2022 **Revised:** 10-Oct-2023
Accepted: 13-Oct-2023 **Published:** 29-Dec-2023

How to cite this article: Mishra P, Bhat J, Yadav R, Sharma RK, Rao VG. Adverse drug reaction patterns of first-line anti-tubercular drugs among Saharia tuberculosis patients: An observational study in particularly vulnerable tribal group of Madhya Pradesh, India. Indian J Public Health 2023;67:542-5.

prospective study to assess the prevalence and patterns of ADRs due to DOTS therapy with drug combinations of first-line anti-TB medications (HRZE) among Saharia TB patients.

The present study was conducted as a part of the "Integrated TB control project" covering more than half-million Saharia population residing in seven districts, i.e., Shivpuri, Sheopur, Ashoknagar, Gwalior, Morena, Datia, and Bhind of Madhya Pradesh state in Central India.

An observational prospective study was conducted to assess the pattern of ADRs of anti-TB therapy defined by National TB Elimination Program (NTEP). The minimum desired sample was estimated as 250, and based on past experiences, it was also estimated with we would have about 850 new TB cases, and during ADR survey about 10% patients might not be available for follow-up surveys, so, every third patients was approached for ADR survey in all districts/block. Overall, during November–December 2019, 857 TB cases were diagnosed and among them 250 who were prescribed Category-I daily DOTS by the physician, were selected ensuring proportional representation of patients from all the study districts and their administrative blocks. Patients with TB were registered for standard daily DOTS treatment at designated centers in the defined area of NTEP. The study was conducted among patients who were on fix dose combinations daily DOTS (HRZE) Category-I therapy for the management of TB and notified in the NIKSHAY under the NTEP.

We assessed the occurrence of ADRs from the anti-TB therapy by conducting home visits in three phases, i.e., first phase (15 days after treatment initiation), the second phase (2 months after treatment initiation during the intensive phase [IP] follow-up), and the third phase (6 months of after treatment initiation during continuation phase (CP) follow-up to near the end of treatment) without any interruption in the DOTS therapy during November 2019–June 2020. At the time of these visits, patients were questioned about any side effects of TB drugs. Interviews were conducted in the local dialect of Hindi by a trained project survey team. Interview tools scheduled for patients covered information about their background, previous history of anti-TB treatment (ATT), date of initiation and completion of treatment, and details of follow-up. During a home visit to patients, any reported adverse effects observed were recorded in the "Adverse Drug Event Reporting Form."

The Institutional Ethics Committee of ICMR-NIRTH, Jabalpur approved the study (NIRTH/IEC/2273/2016). Informed written consent was taken from all the participants in the study.

The collected information was entered in the computer using a data entry software designed especially for the project on CS-PRO platform. Later, the entered data were exported to SPSS (IBM SPSS, 26.0, Armonk, NY: IBM Corp) format for the statistical analysis. Simple descriptive statistical analyses were carried out using SPSS 26.0.

A total of 250 Saharia patients were enrolled in the study. Out of 250 patients enrolled in the study, 247 (98.8%) patients suffered from PTB and 3 (1.2%) patients were extra PTB cases. The age of the patients varied from 10 to 75 years with a mean of 42.8 years and a median of 40.5 years. The majority of study cases were in the age group of 40–59 years (43.2%) and all the study participants (250) were HIV nonreactive. Although both male and female participants equally experienced ADR during the treatment, relatively more females (92.6%) than males (88.6%) reported experiencing ADR during Phase I, whereas more males (57.8%) than females (44.6%) reported experiencing ADR during Phase III.

The frequency of ADRs was found to be higher in the initial phase and gradually decreased. The highest ADRs were recorded in Phase I (89.6%), followed by Phase II (76.4%) and Phase III (54.4%). Higher ADRs were recorded among older patients (≥40 years) compared to younger patients <18 years [Table 1]. More female TB patients experienced ADRs in Phase I (92.3%) compared to male patients (88.6%). Although both male and female participants equally experienced ADR during the treatment, relatively more females (92.6%) than males (88.6%) reported experiencing ADR during Phase I, whereas more males (57.8%) than females (44.6%) reported experiencing ADR during Phase III. Overall, out of 250 patients, 224 patients (89.6%) reported one or more ADRs [Table 1]. The majority of patients suffered from central nervous system (CNS)-related ADRs (75.6%) followed by GI symptoms (74.4%), cardiovascular (49.2%), and dermatological (44.4%) related symptoms during the course of treatment. Shortness of breath (44.8%), vertigo (46.0%), headache (46.8%), nausea (47.6%), vomiting (46.0%), anorexia (31.6%), abdominal pain (32.4%), and itching (41.6%) were common reported ADRs. In the present study, only 26 patients (10.4%) did not experience/report any ADRs in any phase of the course of treatments [Table 2].

The present study reported higher ADRs in a different phase of treatment compared to ADR reported in most of the earlier studies in India and abroad.[7,8] This may be because the present study was in a vulnerable tribal group characterized by the highest TB prevalence along with high alcoholism, smoking, malnutrition, and poor living conditions.[3] All these may be responsible for the enhanced intensity of ADRs.

More female patients experienced ADRs till the end of IP compared with their male counterparts. This could be attributed to the fact that females are at higher risk of developing ADRs as they go through different life stages such as menarche and pregnancy, which may modify their drug response.[9] However, ADR was higher among males (57.8 vs. 44.6) in the continuous phase. This may be because older males are more likely to have higher risk factors such as tobacco smoking and, alcoholism than females. Furthermore, elderly TB patients are often characterized by lower body mass index and malnutrition leading to impaired cell-mediated immune responses toward TB infection. Our findings are also consistent with some other studies in different settings.[10]

The study also revealed that most of the ADRs were noted during the first 2 months of initiation of treatment. This finding

Table 1: Age group wise distribution pattern of adverse drug reactions with anti-tubercular drugs (*n*=250)

Age group	Participants	Number of patients reported ADR, *n* (%)			
		Phase-I	Phase-II	Phase-III	Ever (%)
Age groups					
10–17	06	4 (66.7)	3 (50.0)	2 (33.3)	4 (66.7)
18–39	88	76 (86.4)	64 (72.7)	40 (45.5)	83 (94.3)
40–59	108	99 (91.7)	84 (77.8)	66 (61.1)	104 (96.3)
≥60	48	45 (93.8)	40 (83.3)	28 (58.3)	47 (97.9)
Total	250	224 (89.6)	191 (76.4)	136 (54.4)	238 (95.2)
Sex					
Male	185	164 (88.6)	140 (75.7)	107 (57.8)	176 (95.1)
Female	65	60 (92.3)	51 (78.5)	29 (44.6)	62 (95.4)

ADR: Adverse drug reaction

Table 2: Distribution pattern of adverse drug reactions with anti-tubercular drugs (*n*=250)

Types of ADR	Patterns of ADR, frequency (%)			
	Phase I	Phase II	Phase III	Ever
CNS related				
Vertigo	100 (40.0)	56 (22.4)	17 (6.8)	115 (46.0)
Tinnitus	55 (22.0)	17 (6.8)	8 (3.2)	60 (24.0)
Seizures	10 (4.0)	5 (2.0)	4 (1.6)	16 (6.4)
Visual disturbance	36 (14.4)	39 (15.6)	23 (9.2)	56 (22.4)
Loss of hearing	27 (10.8)	22 (8.8)	14 (5.6)	42 (16.8)
Paresthesia	50 (20.0)	16 (6.4)	14 (5.6)	58 (13.2)
Headache	92 (36.8)	40 (17.2)	36 (14.4)	117 (46.8)
Confusion	34 (13.6)	31 (12.4)	9 (3.6)	46 (18.4)
Any CNS (%)	164 (65.6)	109 (43.6)	79 (31.6)	189 (75.6)
Cardiovascular related				
Shortness of breath	92 (36.8)	55 (22.0)	33 (13.2)	112 (44.8)
Palpitations	28 (11.2)	9 (3.6)	2 (0.8)	33 (13.2)
Any cardiovascular	101 (40.4)	60 (24.0)	34 (13.6)	123 (49.2)
Dermatologic related				
Rashes	40 (16.0)	35 (14.0)	19 (7.6)	64 (25.6)
Itching	77 (30.8)	51 (20.4)	22 (8.8)	104 (41.6)
Any dermatologic	90 (36.0)	65 (26.0)	35 (14.0)	111 (44.4)
GI related				
Nausea	98 (39.2)	68 (27.2)	30 (12.0)	119 (47.6)
Vomiting	99 (39.6)	60 (24.0)	15 (6.0)	115 (46.0)
Anorexia	65 (26.0)	36 (14.4)	12 (4.8)	79 (31.6)
Abdominal pain	68 (27.2)	43 (17.2)	27 (10.8)	81 (32.4)
Diarrhea	33 (13.2)	16 (6.4)	13 (5.2)	41 (16.4)
Any GI	165 (6.0)	126 (50.4)	69 (27.6)	186 (74.4)

ADR: Adverse drug reaction, CNS: Central nervous system, GI: Gastrointestinal

was similar to the study by Sinha *et al*.[7] in which most of the ADRs occurred during the first 2 months of ATT. Thus, the present study emphasized that awareness and motivational counseling of patients regarding the adverse effects of these drugs, timely reporting to the doctor, and arranging follow-up visits are required every week till the end of the IP phase to avoid any unfavorable treatments outcome.

The common ADRs experienced by the patients were CNS and GI-related ADRs. The drugs, which are responsible for these side effects maybe PZA and RFP. The GI disturbance was reported as the most common ADR in other settings as well. Some patients also experienced dermatologic ADRs. The drugs responsible for skin effects may be PZA, RFP, and INH. In the present study population, CNS-related ADRs (vertigo, headache, and short breathiness) and dermatological ADRs were higher than those reported by Priyadarshini *et al*.[10] In the present study, the patients were counseled during the interview and were aided in treatment for ADR. Two of the 250 patients were lost to follow-up. This highlights the need for addressing ADR in this vulnerable group so that they complete the duration of treatment. It is well known that ADR is an important cause for lost to follow-up and impediment to the completion of treatment. NTEP has a format

for ADR reporting and has the guidelines for the prevention and management of ADR. However, this is not done actively and the patients do not come to clinic with ADR, especially in rural area. Hence, it is important that the ADR reporting and referral system may be strengthened by engaging proactively with patients to improve the success rate of treatment among them.

Acknowledgment

The authors are thankful to the Director ICMR-NIRTH, Jabalpur for his support and encouragement throughout the study period. Sincere thanks are due to the project survey team and the district coordinators for carrying out the study in remote tribal villages for their help during the data collection. We are also thankful to the study participants who spared their time and provided valuable information during the study.

Financial support and sponsorship

This work was supported by the Government of Madhya Pradesh (Budget 2210/2017-18/877 dated_27/01/18). The funding agency did not have any role in design of study, data collection, interpretation, and analysis of the results.

Conflicts of interest

There are no conflicts of interest.

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