Section: Pulmonary Medicine

Original Research Article

TO EVALUATE THE FREQUENCY OF ADVERSE MEDICATION RESPONSES ASSOCIATED WITH THE PRESENT TREATMENT REGIMEN FOR MULTIDRUG RESISTANT PULMONARY TB

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Received : 03/11/2023
Received in revised form : 07/12/2023
Accepted : 20/12/2023

Keywords:
ADRs, Pulmonary TB, RNTCP, MDR.

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DOI: 10.47009/jamp.2023.5.6.263

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (6); 1285-1290

Abstract

Background: The management of multidrug resistant pulmonary tuberculosis k(MDR-PTB) poses significant difficulties due to the administration of many anti-TB medications, prolonged treatment duration, and the occurrence of severe adverse drug reactions (ADRs). **Aim:** To evaluate the frequency of adverse medication responses associated with the present treatment regimen for multidrug resistant pulmonary TB. **Material & Methods:** A total of 150 patients with proven multidrug-resistant (MDR) pulmonary tuberculosis were admitted to the hospital for pre-treatment assessment according to the guidelines of the Programmatic management of Drug-Resistant tuberculosis in india(PMDT) and were thereafter monitored. The adverse drug reactions (ADRs) of all patients were monitored on a daily basis during their hospital stay, and this monitoring continued even after the patients were discharged until the conclusion of their therapy. Hartwig's severity evaluation levels were used to evaluate the severity of ADRs. The patients experiencing severe ADRs were consistently followed up by consulting the relevant departments. **Results:** ADR was seen in 120 (80%) participants out of 150 in our research. A total of 15 kinds of ADRs were recorded. The prevalence of gastrointestinal upset was reported in 98 cases (81.67%), making it the most prevalent symptom. This was followed by joint pain in 68 cases (56.67%) and headache in 57 cases (47.5%). The ADR Hartwig's scale was used for the assessment, and a majority of the patients (66.67%) had level three responses. 48 (40%) of the patients had four or more kinds of responses. Among the 120 patients afflicted by ADR, 72 individuals (60%) had relief in symptoms by symptomatic therapy, eliminating the requirement for medication withdrawal. 41 individuals, accounting for 34.17% of the total, necessitated discontinuation of the problematic medication and substitution with an alternative. Eleven patients, accounting for 10.83% of the total, were only treated with counselling and assurance. **Conclusion:** The majority of ADRs may be managed by symptomatic treatment. The prevailing symptoms were gastrointestinal discomfort, followed by joint pain and headache. The occurrence of significant side effects such as damage to the ears and neurological signs may result in the discontinuation of essential medications from the treatment plan. Therefore, it is important to provide counselling on these crucial signs and to thoroughly explain the treatment strategies in a proactive manner.

INTRODUCTION

Tuberculosis is one of the top 10 causes of mortality globally and has been the leading cause of death from a single infectious agent since 2007.[1] In 2019, there were about 11 million new cases of tuberculosis worldwide, resulting in 1.3 million fatalities attributable to TB. Southeast Asia and

Africa were responsible for 44% and 25% of these deaths, respectively.[1] Uganda has a significant prevalence of TB, with an estimated occurrence of 200 cases per 100,000 people, and a corresponding death rate of 35 per 100,000 people.[2] In 2018, India accounted for 25% of the worldwide TB burden, with an estimated 2.7 million new cases. The Indian government has established an ambitious objective of achieving a TB-free India by 2025, which is five years earlier than the worldwide aim of 2030.[3]

Multidrug-resistant tuberculosis (MDR-TB) is a kind of tuberculosis that is resistant to at least rifampicin and isoniazid. The worldwide prevalence of MDR-TB is 3.3% among newly diagnosed cases of tuberculosis, and 18% among those who have been previously treated for tuberculosis.[1] The prevalence of MDR-TB in sub-Saharan Africa is estimated to be 2.1% among individuals who have newly contracted TB. The incidence rate in Uganda is around 1.6% for new cases of tuberculosis and 12% for patients that have been previously treated.[3,4] Second-line medicines have effectively controlled MDR-TB in the setting of excellent adherence. Nevertheless, these secondary medications have a tendency to be toxic, and their extended period of use makes patients more susceptible to adverse drug reactions (ADRs).[5] Nevertheless, the use of shorter duration (9–12 months) and more bearable treatment plans has significantly changed the way clinical research and management of multidrug-resistant tuberculosis (MDR-TB) are approached.[6]

An adverse drug reaction (ADR) is defined by the World Health Organisation (WHO) as a harmful and unanticipated response to a medication, which occurs at levels typically used in humans for disease prevention, diagnosis, treatment, or physiological function alteration/.[7] ADRs caused by medications used to treat MDR-TB are a significant issue for public health. The estimated worldwide incidence of these ADRs is greater (ranging from 8% to 85%) among patients who are using first-line treatments, compared to those who are taking second-line drugs (ranging from 69% to 96%). Approximately 83% of patients undergoing treatment for MDR-TB in Africa encounter at least one ADR over the course of their therapy. Specifically, Kenya and Ethiopia record prevalence rates of 61% and 98.6%, respectively.[8] The most common ADRs seen in patients undergoing therapy for MDR-TB are skin responses, gastrointestinal reactions, respiratory symptoms, liver damage, kidney damage, hearing loss, musculoskeletal problems, and neurological problems.[9] While the majority of ADRs are minimal and do not need stopping or discontinuing therapy, it is important to promptly identify and treat severe or life-threatening ADRs in order to consider. modifying or discontinuing MDR-TB treatment.[10] Furthermore, ADRs not only lead to non-compliance with medication, but also contribute to unfavourable consequences such as prolonged hospitalisation and severe illness.[11]

MATERIALS AND METHODS

This research was conducted at the Department of Respiratory Medicine as a cross-sectional observational study. A total of 150 patients with proven multidrug-resistant (MDR) pulmonary tuberculosis were admitted to the study hospital for pre-treatment assessment according to the guidelines of Programmatic management of drug resistant tuberculosis in india and were thereafter monitored. The study excluded patients who had previously experienced an allergic reaction to any medication, as well as those with a history of central nervous system disorders, peripheral neuropathy, psychiatric disorders, dermatological diseases, HIV infection, and hepatitis B or C. Additionally, patients with abnormal results in their initial evaluations were also excluded.

Methodology

The informed permission and comprehensive medical history of each patient were gathered, focusing on symptoms such as prolonged fever, persistent cough for more than two weeks, chest discomfort, reduced appetite, weight loss, night sweats, body swelling, decreased urine output, pedal edema, and shortness of breath. The patient's age, gender, and weight were recorded. A comprehensive physical examination and essential laboratory procedures were conducted to exclude the presence of any other concurrent medical conditions. Prior to commencing treatment, patients underwent pre-treatment assessment including sputum smear, liver function tests, kidney function tests, thyroid function tests, blood sugar levels, psychiatric evaluation, HIV status, chest X-ray, urine analysis for albumin and sugar, and pregnancy test for female patients. Additionally, electrocardiography (ECG) and audiometry were conducted to assess for any pre-existing cardiac and otic abnormalities.

Following the receipt of CBNAAT findings and other drug susceptibility testing, the patients were treated in accordance with the Programmatic Management of DR-TB guideline. The administration of medication doses was based on weight categories in accordance with the National Tuberculosis Elimination Programme(NTEP) and PMDT. The adverse drug reactions (ADRs) of all patients were monitored on a daily basis during their hospital stay, and this monitoring continued even after the patients were discharged until the conclusion of their therapy.

The occurrence of any adverse effects after the initiation of MDR-TB therapy was documented and assessed. Any negative consequences that occurred during the treatment period were documented. Throughout the therapy process, the patients were monitored using radiological and laboratory examinations. Any negative responses were identified based on clinical and/or analytical criteria. Hartwig's severity evaluation levels were used to evaluate the severity of ADRs. The patients

ISSN (O): 2687-5365; ISSN (P): 2753-6556

experiencing severe ADRs were consistently followed up by consulting the relevant departments.

Statistical Analysis

The data analysis was conducted using SPSS software version 25.0. The findings were examined using descriptive statistics and presented as percentages.

RESULTS

ADR was seen in 120 (80%) participants out of 150 in our research. A total of 15 kinds of ADRs were recorded. A significant proportion of the patients (56.67%) were between the age range of 30-40 years, making it the predominant age group in our research. The male-to-female ratio in our research was 2.33:1. A total of 105 patients were recorded in the weight range of 30-45 kg, which had the highest number of patients. Adverse drug reactions (ADR) were more prevalent among those aged 30–40 years and 40–50 years. Nevertheless, the Fisher's exact test yielded a p-value of 0.15, indicating that there is no statistically significant difference. Adverse drug reactions (ADRs) were most often found in individuals weighing between 45 and 60 kilogrammes. There was no discernible association between weight and ADR. The provided information is shown in Table 1

The prevalence of gastrointestinal upset was reported in 98 cases (81.67%), making it the most prevalent symptom. This was followed by joint pain in 68 cases (56.67%) and headache in 57 cases (47.5%). Other symptoms included insomnia in 38 cases (31.67%), depression in 32 cases (26.67%), ototoxicity in 24 cases (20%), peripheral neuropathy in 12 cases (10%), and dermatological issues in 10 cases (8.33%) [Table 2].

The ADR Hartwig's scale was used for the assessment, and a majority of the patients (66.67%) had level three responses, as seen in Table 3. Table 4 shows that 48 (40%) of the patients had four or more kinds of responses. Among the 120 patients afflicted by ADR, 72 individuals (60%) had relief in symptoms by symptomatic therapy, eliminating the requirement for medication withdrawal. 41 individuals, accounting for 34.17% of the total, necessitated discontinuation of the problematic medication and substitution with an alternative. Eleven patients, accounting for 10.83% of the total, were only treated with counselling and assurance, as shown in Table 5.

The majority of patients experiencing adverse effects in the central nervous system were treated by increasing the dosage of pyridoxine and introducing amitriptyline, pregabalin, and methylcobalamin. Two patients underwent substitution of cycloserine with PAS owing to the development of profound neuropathy. 10 individuals (8.33%) suffered dermatological adverse effects. The majority of cases reported symptoms of pruritus, and four individuals had the manifestation of dermatitis. The bad effects were mitigated with the use of antihistamine drugs, such as chlorpheniramine, and consultation with a dermatologist. No medicines were discontinued in these individuals.

A total of 9 individuals, accounting for 7.5% of the sample, had hypothyroidism. One patient had ethionamide treatment halted and received management based on an endocrinologist's judgement. Most patients were started on a dosage of 25-50 mg of thyroxine, as recommended by endocrinologists. Two individuals developed hepatitis and were treated symptomatically. Pyrazinamide and Ethionamide were halted for a duration of 2 weeks. 5 patients, accounting for 4.17% of the total, had their hepatitis therapy discontinued. The whole medication regimen was resumed in these individuals, and therapy was effectively delivered. Three patients (2.5%) had visual problems, leading to the permanent discontinuation of ethambutol and referral to ophthalmologists. Renal toxicity, characterised by a little increase in creatinine levels compared to the initial baseline, was detected in two patients.

Table 1: Basic profile with developed ADR

	Patients=150	Percentage	DevelopedADR =120		P value
Gender			**Number**	**Percentage**	**0.24**
Male	105	70	85	66.67	
Female	45	30	35	33.33	
Age in years					
below 30	17	11.33	13	76.47	0.15
30-40	85	56.67	70	82.35	
40-50	39	26	30	76.92	
Above 50	9	6	7	66.67	
Mean Age	38.85±4.25				
Weight in kg					**0.19**
below 30	8	6.67	6	75	
30–45	105	70	83	79.05	
45–60	34	22.67	29	85.29	
Above 60	3	2	2	66.67	
Smoking status					0.17
No	80	53.33	65	81.25	
Yes	70	46.67	55	78.57	

Table 2: Types of ADRs

ADR	Number of Patients =120	Percentage

ISSN (O): 2687-5365; ISSN (P): 2753-6556

ADR		
Gastrointestinal upset	98	81.67
Joint pain	68	56.67
Headache	57	47.5
Insomnia	38	31.67
Depression	32	26.67
Ototoxicity	24	20
Peripheral neuropathy	12	10
Dermatological	10	8.33
Psychosis	9	7.5
Hypothyroidism	9	7.5
Hepatitis	5	4.17
Suicidal ideation	5	4.17
QT Prolongation	4	3.33
Visual disturbances	3	2.5
Nephrotoxicity	2	1.67

Table 3: Modified Hartwig and Siegel scale for severity assessment of ADRs

Severity	Level	Number	Percentage
Mild	Level 1	8	6.67
	Level 2	0	0
	Total	8	6.67
Moderate	Level 3	80	66.67
	Level 4	17	14.17
	Total	97	80.83
Severe	Level 5	00	
	Level 6	15	12.5
	Level 7	00	
	Total	15	12.5

Table 4: Number of ADRs among patients

Number of ADRs	Number of patients	Percentage
1	13	10.83
2	19	15.83
3	40	33.33
≥4	48	40

Table 5: ADR management

ADR Management	Number of Patients	Percentage
Symptomatic	72	60
Discontinued drug	41	34.17
Treatment not required	13	10.83

DISCUSSION

India has been classified as a nation with a significant prevalence of pulmonary tuberculosis, multidrug-resistant tuberculosis, and tuberculosis co-infected with HIV.Drug resistant TB provide significant challenges in terms of therapy, since they need extended administration of less effective and more toxic medications. ADRs linked to these medications add complexity to the situation, leading to patients discontinuing treatment, inadequate therapy, and thereby impacting the success rate. Effectively managing ADRs and addressing the associated treatment costs are crucial aspects that need attention.[12] ADR was seen in 120 (80%) participants out of 150 in our research. A total of 15 kinds of ADRs were recorded. The prevalent adverse effects were gastrointestinal disturbance, arthralgia, and cephalalgia. Drug regimen modification was necessary in 41 out of 120 patients, accounting for 34.17% of the total. Approximately 13 patients, accounting for 10.83% of the total, terminated their therapy as a result of unfavourable consequences. Gastrointestinal distress and arthralgia were the prevailing symptoms in prior investigations as well.[13-15]

In a study conducted by Patel et al,[16] at Smt. N.H.L. Municipal Medical College in Ahmedabad, India, it was found that out of 142 patients, 78 experienced ADRs. The most frequently reported side effects after 6 months and 24 months of therapy were gastrointestinal disturbances, headaches, and arthralgias. A modification of the medication regimen was necessary in 9.84% of patients at the first follow-up, 5.97% during the second follow-up, and in 4.47% of patients at the 24th month of therapy, resulting in a reduction in drug dosage. In a separate investigation conducted by Pawar et al,[15] it was shown that out of the 120 patients observed, a total of 117 (97.5%) individuals encountered one or more ADRs during the intensive phase. The predominant adverse response seen was gastrointestinal side effects, reported by 85 individuals (72.6%), followed by joint discomfort, reported by 66 individuals (56.4%). 11 (9.1%) individuals had their treatment regimen adjusted during the intense phase owing to medication toxicity. In a separate trial carried out by Yang et

ISSN (O): 2687-5365; ISSN (P): 2753-6556

al,[17] in South Korea, 37.1% of the 256 patients had one or more adverse symptoms. The research found that the most prevalent adverse effects were gastrointestinal disturbance (18.4%), mental problem (5.5%), and arthralgia (4.7%). A total of 54 individuals necessitated discontinuation of medication therapy, mostly owing to adverse effects of PAS, followed by cycloserine and kanamycin.

According to a research done by Bhardwaj et al,[18] 83.33% of all patients had at least one sort of adverse response. The most prevalent adverse effects of this medication were gastrointestinal issues (76% of patients had them), mental symptoms (44.7%), arthralgia and hyperuricemia (31.3%), central nervous system problems (22.7%), and ototoxicity (22%). Eleven individuals need a modification in their treatment plan, while five patients discontinued therapy during the continuation phase due to the adverse effects of cycloserine. Shinde et al,[19] shown that among 468 individuals, 60 (12.82%) had at least one side event and required hospitalisation as a result. Out of the 109 documented ADRs, the most frequently reported ADR was gastrointestinal discomfort, accounting for 5.98% of the cases. Other commonly reported ADRs were psychosis (4.91%) and ototoxicity (2.99%).

A research done by Bhatt and Kc,[20] in Nepal examined MDR patients and identified unfavourable effects in 101 individuals. The predominant side effects seen were arthralgia (21.2%), nausea (20.3%), otological impairments (11%), gastrointestinal disturbances (9.9%), and a subset of 22 patients (18%) had severe adverse reactions necessitating discontinuation of the implicated medication(s). Cycloserine induced significant psychotic adverse events in 15 patients, leading to its discontinuation in these individuals. Hearing loss led to the discontinuation of Kanamycin in five individuals due to severe adverse effects.

Consistent with the aforementioned research, the present investigation likewise identified gastrointestinal symptoms as the most prevalent. The symptoms were successfully alleviated with counselling and the use of a proton pump inhibitor. Drug administration was halted for a duration of 1-2 weeks in some individuals due to suspected drug use. In a research performed by Shinde et al,[19] and Pawar et al,[15] it was found that the most often implicated medicines were ethionamide and pyrazinamide. Another study by Yang et al,[17] revealed that out of 47 patients, 29 required removal of the drug PAS due to its causal effects. In a separate research done by Furin et al,[21] and Nathanson et al,[13] it was shown that PAS is primarily responsible for gastrointestinal discomfort. 68 individuals, accounting for 56.67% of the total, had joint discomfort. Pyrazinamide was halted for a duration of 2 weeks in a group of 20 patients. Pyrazinamide and levofloxacin were the medications responsible for the adverse effects. The symptoms of Hyperuricemia were managed with a dosage of 40 mg of Febuxostat administered twice daily. Nonsteroidal anti-inflammatory medicines were used to alleviate the symptoms. Nevertheless, pyrazinamide was discontinued in 3 individuals. The medications cycloserine, fluoroquinolones, and ethionamide are responsible for ADRs affecting the central nervous system (CNS), such as psychosis, seizures, headache, sleeplessness, and suicidal thoughts. Cycloserine was identified as the primary causative agent for psychosis and depression. Prior research has shown increased prevalence of psychosis and depression.[22,23] The variation may be attributed to the administration of a consistent and elevated dosage of cycloserine (1000 mg) in the subjects included in these investigations. The majority of patients had positive responses to counselling, whereas a portion of the cases were managed with antidepressant medications such as clonazepam and escitalopram. Cycloserine was typically discontinued for a brief duration of time, ranging from 1 to 4 weeks. Six individuals have had permanent discontinuation of Cycloserine. Out of the total number of patients, 9 had severe psychosis, while 5 acquired suicidal thoughts. These conditions were addressed by prescribing antipsychotic drugs recommended by a psychiatrist. Psychiatric illnesses (5.5%) were a significant contributing factor to the drug's withdrawal, as seen in the research conducted by Yang et al,[17] Twenty-four out of 120 individuals had ototoxicity, which is a typical adverse event. The majority of subjects had varied degrees of hearing loss. Aminoglycosides must be discontinued because of their ototoxicity and substituted with PAS. In previous investigations conducted by Yang et al,[17] and Piparva,[23] et al., ototoxicity was identified as the second most prevalent adverse impact.

Torun et al,[24] showed a significantly elevated incidence of ototoxicity (41.8%), which may be attributed to the administration of a larger dosage (1000 mg) of aminoglycosides and the longer duration of therapy lasting up to one year. Moore et al. established a correlation between ototoxicity and the length of time aminoglycosides are used, which aligns with the results of the prior research,[25] 12 patients, accounting for 10.71% of the total, had peripheral neuropathy, which manifested as a feeling of pins and needles, numbness, or pain in the hands or feet, with or without accompanying symptoms. Bhardwaj et al. reported peripheral neuropathy in 18.7% of the patients in their research. The number 18 is enclosed in square brackets. The inclusion of pyridoxine in the treatment regimen for patients may have contributed to a lower incidence of peripheral neuropathy compared to previous trials. The management of adverse consequences of hepatitis (3.57%) in other recent research involves symptomatic therapy. The interval,[18,20] The inclusion of even the slightest symptoms, such as nausea, in our investigation may explain the elevated occurrence of ADR seen in the current study.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

ADRs are the primary factor leading to the early discontinuation of therapy in several individuals. Furthermore, ADR might result in an escalation in treatment expenses and frequent admissions to the hospital as well. Defaulter patients of this kind are at a heightened risk of recurrence and treatment failure. Therefore, any small adverse effect should be addressed with symptomatic management, but therapy should be maintained. If a serious adverse drug reaction (ADR) occurs, it is necessary to substitute the causative medicine with an alternative medication and modify the treatment plan accordingly. It is necessary to regularly monitor and address any significant ADRs and hospitalisation may be required for patients experiencing such reactions.

CONCLUSION

Over 50% of the individuals in this trial had ADRs. The majority of ADRs may be managed by symptomatic treatment. The prevailing symptoms were gastrointestinal discomfort, followed by joint pain and headache. The occurrence of significant side effects such as damage to the ears and neurological signs may result in the discontinuation of essential medications from the treatment plan. Therefore, it is important to provide counselling on these crucial signs and to thoroughly explain the treatment strategies in a proactive manner. By continuously monitoring patients in the intense phase of therapy and promptly identifying ADRs, we may effectively reduce morbidity.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556