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Original Research Article

A study of adverse drug reactions in patients receiving treatment for multi-drug resistant tuberculosis

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ABSTRACT

Background: A high frequency of adverse drug reactions (ADRs) is one of the major challenges in the treatment of Multi-drug resistant tuberculosis (MDR-TB). Patients may refuse to continue treatment if ADRs are not properly addressed, drugs may be stopped unnecessarily and treatment may be terminated prematurely by inexperienced health workers, resulting in a high proportion of failure.
Methods: Patients diagnosed for MDR-TB and registered in Drug Resistant TB centre (DR-TB) of tertiary care hospital during period of July 2014 to June 2015 were enrolled in the study. Data of patients hospitalized for the complaints of ADR in DR-TB centre during study period was collected.
Results: Out of 468 patients, 60 (12.82%) patients developed at least one adverse reaction and were hospitalised for the same. Among 109 reported ADRs, Gastrointestinal upset was the most common ADR reported (5.98%) followed by psychosis (4.91%) and ototoxicity (2.99%).
Conclusions: The health providers, the patients and their relatives should be sensitised about these ADRs for early detection and treatment. It can also be suggested that the setup of DR-TB centre should be integrated with psychiatry and ENT specialities, with all the provisions of early detection of ADR and treatment.

Keywords: ADR, Drug resistance, MDR-TB, Tuberculosis

INTRODUCTION

Drugs can be remarkably beneficial, lengthen life and improve life quality by reducing symptoms and improving well-being. However, all drugs have adverse effects and carry the potential for causing injury, even if used appropriately.[1] Multidrug-resistant Tuberculosis (MDR-TB) is caused by organisms that are resistant to at least the two most effective anti-TB drugs, isoniazid and rifampicin. These MDR strains require prolonged treatment using second line drugs which are highly toxic and less effective.[2]

The Revised National TB Control Programme (RNTCP) has launched "Directly Observed treatment Short-Course (DOTS) Plus" for management of drug resistant tuberculosis (DR-TB) in 2007 and has expanded these services to all states and Union Territories across the country in 2012. Standardized treatment regimen for MDR-TB under daily DOTS-Plus includes 6-9 months Intensive Phase (IP) drug therapy and 18 months Continuation Phase (CP) drug therapy.[3]

A high frequency of adverse drug reactions is one of the major challenges in the treatment of MDR-TB. Patients may refuse to continue treatment if adverse drug reactions are not properly addressed, drugs may be stopped

unnecessarily and treatment may be terminated prematurely by inexperienced health workers, resulting in a high proportion of failure. It is essential to monitor adverse drug effects in a systematic and timely manner. A comprehensive knowledge regarding patterns, severity, causative agents and ultimate health effects generated from active, prospective surveillance clearly has important implications for effective RNTCP.

METHODS

Study design

It was a prospective observational study conducted at the Pulmonary Medicine Department of tertiary care hospital during the period of July 2013 to June 2015, after approval by Institutional Ethics Committee and Department of Pulmonary Medicine.

Data collection

The definition of adverse drug reaction used in this study is the one provided by the WHO.[4] During study period, data of patients receiving MDR-TB treatment hospitalized in DR-TB Centre of a teaching tertiary care hospital, for the complaints of ADR was collected from patients medical and nursing records regarding age, sex, height, weight, pregnancy, co-morbid illness such as diabetes mellitus, hypertension, dose and duration of MDR-TB drugs, other medications, investigations such as complete blood count, liver function tests (LFT), renal function tests (RFT), etc. were obtained after taking written informed consent of patients. Data of patients reported with ADR to MDR-TB treatment and managed at peripheral centers were not included in the study. According to weight, patients were categorized into Band I, Band II and Band III as per Programmatic Management of Drug Resistant Tuberculosis (PMDT).[5]

All MDR-TB patients under the study routinely received following drugs as per Programmatic Management of Drug Resistant Tuberculosis.[5]

Table 1: Regimen for MDR TB dosage and weight band recommendations.

Sr. No	Drugs	Band I (16-25 Kgs)	Band II (26 -45 Kgs)	Band III (46-70 Kgs)
1	Kanamycin	500mg	500mg	750mg
2	Cycloserine	250mg	500mg	750mg
3	Levofloxacin	250mg	750mg	1000mg
4	Ethionamide	375mg	500mg	750mg
5	Ethambutol	400mg	800mg	1200mg
6	Pyrazinamide	500mg	1250mg	1500mg
7	Pyridoxine	50mg	100mg	100mg
8	PAS (only in cases of drug intolerance)	5gm	10gm	12gm

Statistical analysis

Data was entered into MS-Exel sheet**.** Descriptive statistics was used to analyze the data. Results were expressed as either percentage or mean ± standard deviation (SD). Mean ± standard deviation was calculated by using Graph pad prism 5.02.

Severity of adverse drug reactions was assessed by using Modified Scale of Hartwig and Siegel into mild, moderate and severe category.[6] Causality assessment of adverse reaction was done according to Naranjo's Causality Algorithm into definite, probable and possible category.[7]

RESULTS

A total of 468 patients with diagnosed MDR-TB and receiving MDR-TB therapy were enrolled in the study. The mean age of the study population was 34.58±13.03 years and 60.04% patients were male. Mean weight of the study population was 42.42±9.72 kgs. Majority of patients belongs to weight band II (63.68%). Out of 468 patients, 60 (12.82%) experienced at least one ADR. Total number of ADRs observed in 60 patients was 109 (Table 2).

Table 2: Demographic characteristics of MDR-TB patients (n=468).

Characteristics	Value
Total numbers of patients on MDR-TB treatment	468
Age (years)	
Mean ± SD	34.58 ± 13.03
Range	10-75
Gender	
Male	287 (61.32%)
Female	187 (38.68%)
Weight (kgs)	
Mean ± SD	42.42 ± 9.72
Range	16-70
Weight bands (kgs)	
Band I(16-25)	15 (3.20%)
Band II (26-45)	298 (63.68%)
Band III (46-70)	155 (33.12)
Number of patients reporting ADR	60 (12.82%)
Number of total ADRs	109

Values are expressed as Mean ± Standard deviation (SD) or number (%); ADR: adverse drug reaction.

The demographic characteristics of patients (n=60) experienced at least one ADR were shown in the Table 3. The incidence of ADRs was higher in males (56.67%) as compared to females (43.33%) and mean age of the study population was 35.27±12.10 years. Majority of patients (56.67%) belongs to weight band II.

Among 109 reported ADRs, Gastrointestinal upset (nausea, vomiting) was the most common ADR reported

(5.98%) followed by psychosis (4.91%) and ototoxicity (2.99%) (Table 4).

Table 3: Demographic characteristics of patients experienced at least one ADR.

Characteristics	Value
Numbers of patients experiencing ADR (n)	60
Age (years) Mean Range	 35.27±12.10 19-68
Gender* Male Female	 34 (56.67%) 26 (43.33%)
Weight (kg) Mean Range	 42.78 ± 10.81 22-70

Mean ± Standard deviation (SD) or number (%)

Table 4: Details of 109 ADRs in 468 patients receiving MDR-TB therapy.

Adverse drug reaction	Number of patients with ADR (%)*	Action taken for ADR
Gastrointestinal upset	28(5.98)	Symptomatic treatment
Psychosis	23(4.91)	Cs replaced by PAS (n=17), antipsychotics started
Ototoxicity	14(2.99)	Km replaced by PAS (n=14)
Insomnia	7(1.49)	Symptomatic treatment
Arthralgia	7(1.49)	Symptomatic treatment
Giddiness	7(1.49)	Symptomatic treatment
Depression	6(1.28)	Antidepressants started
Headache	4(0.85)	Symptomatic treatment
Skin rash	4(0.85)	Symptomatic treatment
Peripheral neuropathy	2(0.43)	Additional tab pyridoxine 100 mg given per day
Gynaecomastia	2(0.70)	Ethionamide replaced by PAS (n=2)
Suicidal ideation	2(0.43)	Antidepressants started
Convulsions	1(0.21)	Lvx replaced by PAS, anticonvulsant started
Acne vulgaris	1(0.21)	Symptomatic treatment
Visual disturbances	1(0.21)	Ethambutol stopped and PAS added

On doing Severity assessment of ADRs by using modified Hartwig and Siegel scale, 51.38% reactions were 'Moderate' (level 4b) and 35.78% were of 'Mild' category (level 1) (Table 5).

Table 5: Severity assessment of ADRs (n= 109) by modified Hartwig and Siegel scale.

Severity	Level	Number (%)
Mild	Level 1	39 (35.78)
	Level 2	0
	Total	39 (35.78)
Moderate	Level 3	00
	Level 4a	00
	Level 4b	56 (51.37)
	Total	56 (51.38)
Severe	Level 5	00
	Level 6	14 (12.84)
	Level 7	00
	Total	14 (12.84)

Casualty assessment of all ADRs was done by using Naranjo's causality assessment scale, 60.55% adverse reactions were 'Possible' category while 39.45% were 'Probable' category (Table 5).

Table 6: Causality assessment of ADRs (n=109) Naranjo's causality algorithm scale.

Causality	Number (%)
Definite	00
Probable	43 (39.45)
Possible	66 (60.55)

DISCUSSION

Drugs for treating MDR-TB strains involve a long-term exposure and have greater toxicity effects. A high frequency of adverse drug reactions is one of the major challenges in the treatment of MDR-TB. The present study evaluated pattern and frequency of adverse drug reactions in patients receiving treatment for Multi-drug resistant tuberculosis, and assessed their severity and causality.

The demographic characteristics of patients receiving treatment for MDR-TB (Table 2) in present study were comparable to the previous study conducted by Kapadia et al.[8]

In the present study, 60 (12.82%) patients developed at least one adverse reaction and were hospitalized for the same. The total number of ADRs shown by 60 patients was 109, as more than one ADR was observed in 27 (45%) patients. The percentage of patients showing ADR to MDR-TB therapy in the present study was lower than that reported in the some of the previous studies, which could be due to use of PAS as primary drug in their regimens.[9-11] In addition, ADRs were reported through real time spontaneous reporting system by physician in study conducted by Shin et al.[10] Whereas, in the present study data of only patients hospitalized for complaint of ADR were gathered. This could have resulted in under-

reporting of minor ADRs like GI upset in some of the patients. Higher rate of ADRs in the study conducted by Torun et al as compared to the present study could be due use of aminoglycosides for longer duration (up to 12 months).[11] In addition to prolonged hospital stay (till initiation of continuation phase) once monthly monitoring after the discharge of the patients in their study possibly has facilitated reporting of more number of ADRs.

Table 4 shows details of ADRs observed in the present study. Gastrointestinal upset namely nausea, vomiting was the most common adverse drug reaction (5.98%). All these patients were treated symptomatically and none of the patients required drug withdrawal. The causative drugs in PMDT regimen were PAS, ethionamide, pyrazinamide and ethambutol. Gastrointestinal upset was the most common ADR reported in the earlier studies.[8-10] As compared to previous studies, the occurrence of GI upset in the present study is lower. This can be explained on the basis that our data included hospitalized patients with a possibility of minor GI upset ADR in some patients would have been observed and treated by health providers working at the periphery. In addition to this higher rates of gastrointestinal upset in Furin et al and Shin et al studies, could be due PAS administered as primary drug in regimen as mentioned above.[9,10] In our study PAS was used only as a replacement drug in case of drug withdrawal.

In the present study the most commonly affected system was central nervous system. Adverse drug reactions related to CNS were psychosis, depression, insomnia, headache, suicidal thoughts and convulsions. The common offending drugs were cycloserine, fluoroquinolones and ethionamide. In the cases of psychosis, depression and suicidal thoughts, the first offending drug was cycloserine. Psychosis is an important concern with MDR-TB therapy. It was the second most common ADR in our study (Table 4). Higher rates of psychosis and depression have been reported in the previous studies.[9,10] This discrepancy could be due to fixed and higher dose of cycloserine (1000mg) used in their patients. As opposed, in our study dose of cycloserine was not fixed and lower doses (250-750mg) were used with due consideration to different weight bands. The mean duration of onset of psychosis was higher as compared to other studies.[9,10] The higher mean interval in the present study indicates delayed onset of psychosis which could be due to lower dose and weight band wise titration of dose of cycloserine, as opposed to fixed and higher dose of cycloserine used in the previous studies as mentioned above. Another possibility is of delayed reporting. In the present study all patients showing psychosis were treated with antipsychotic drugs. Psychosis was the most common ADR leading to drug withdrawal.

Otovestibular system related ADRs in the present study were ototoxicity and giddiness. Ototoxicity was the third most common ADR in our study (Table 4). A clear association of ototoxicity with use of kanamycin and other aminoglycosides has been proven.[12] Very high rate of ototoxicity was reported by Torun et al (41.8%) could be attributed to the higher dose (1000mg) and extended exposure (upto 12 months) to aminoglycosides in their study.[11] This is consistent with findings by Moore et al, who showed an association between ototoxicity and cumulative duration of aminoglycosides.[12] In all patients with ototoxicity, kanamycin was replaced by PAS. Ototoxicity was the second most common ADR resulting in drug withdrawal.

Pyrazinamide and levofloxacin can cause arthralgia. The occurrence of Arthralgia in the present study is lower (Table 4) as compared to the previous studies.[8-11] It is possible that in some of our patients receiving MDR-TB therapy, artralgia was treated in the periphery by health supporters, resulting in under-reporting.

Use of ethionamde, levefloxacin and pyrazinamide are associated with dermatological ADRs (rashes and acne vulgaris). The percentage of ADRs related to dermatological system is similar to reports by Kapadia et al (1.58%).[8] Higher rates of ADR related to dermatological system were reported by some of the previous studies.[9-11]

Ethionamide can cause gynaecomastia and peripheral neuropathy. Two cases of gynacomastia were reported in the present study (Table 4). The large sample size of our study as compared to previous similar studies could have facilitated detection of this uncommon ADR.

The percentage of peripheral neuropathy observed in the present study (Table 4) is lesser as compared to the previous studies. In these studies pyridoxine was either not used or used in lower dose.[9-11]

Antitubercular drugs can cause hepatotoxicity. Hepatotoxicity was not reported in the present study. The wide variation in rates of hepatotoxicity reported in the literature could be attributed to different drugs used in different regimen of different studies, host factors, environmental factors, genetic predisposition, varying definition of hepatotoxicity and inability to exclude other causes of hepatotoxicity.[13]

In order to take proper initiatives towards the management of ADRs, it is necessary to study the severity of ADRs. Modified Hartwig and Siegel scale is widely used for this purpose, which categorizes ADRs into mild, moderate and severe. In the present study 51.38% of ADRs were 'Moderate' (level 4b) and 35.78% were of 'Mild' category (level 1) (Table 5).

Carrying out the casualty assessment using standard methods is one of the best ways to establish the casual relationship between a drug and adverse event. In the present study, on doing causality assessment by using Naranjo's causality assessment scale, 60.55% of ADRs

were belonging to 'Possible' category while 39.45% 'Probable' category (Table 6).

Strength of our study is inclusion of all hospitalized patients complaining of ADRs to MDR-TB treatment over period of two years at single centre where the protocol for management of the patients could be expected to be uniform. In addition to this data of present study is prospective. There are however, certain limitations to our study. The results of this study could not be generalized to patients receiving MDR-TB therapy in community. Further studies with larger sample size needs to be carried out.

CONCLUSION

The percentage of patients showing ADR to MDR-TB therapy in the present study is lower than that reported in the previous studies due to use of different weight bands. Psychosis and ototoxicity are major concerns in the successful management of MDR-TB as they commonly lead to drug withdrawal, poor patient compliance and use of less efficient drugs in the regimen. Hence we recommend, the health care providers, patients and their relatives should be sensitized about these ADRs for early detection and treatment. It can also be suggested that the setup of DR-TB centre should be integrated with psychiatry and ENT specialties, with all the provisions of early detection of ADR and treatment. As most of ADRs are related to amount of drug in the body, therapeutic drug monitoring should be made an essential element of the programme.

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