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Original Research Article

Frequency and type of adverse drug reactions related to multidrug-resistant tuberculosis therapy

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ABSTRACT

Background: Adverse drug reactions (ADRs) are inevitable consequences of multidrug-resistant tuberculosis drug therapy. Reporting of ADR in India is poor and inadequate. ADRs monitoring forms an integral part of pharmacovigilance. ADRs with second line anti-tuberculous therapy (ATT) have been mentioned as obstacles in the management of multidrug-resistant tuberculosis (MDR-TB). Objectives of the study was to study the frequency and type of adverse drug reaction related to MDR-TB therapy.
Methods: 72 patients diagnosed as MDR-TB and enrolled for DOTS-PLUS (CAT.IV) regimen at NTEP centre, KIMS HUBLI were included. This was a prospective observational study. All patients were followed up for a period of 9 months from the day of commencement of treatment. Adverse drug reactions were determined by monthly clinical and biochemical monitoring of patients to identify ADRs.
Results: Among 72 Patients, 42 (58.3%) were males. 44 out of 72 patients experienced at least one type of ADRs (61.1%). Mean age was 35.86±12.62 and mean weight was 42.00±9.05. Four most common ADRs reported were Gastro-intestinal symptoms (29.2%), anorexia (15.3%), giddiness (12.5%), and pain at injection site (11.1%). Highest percentage of ADRs were seen in patients of age group>60 years (66.7%). ADRs were most commonly reported in first 3 months of initiation of therapy. 9 out of 72 patients (12.5%) or 20.5% of 44 patients who showed ADRs required change of treatment. There was a significant impact of ADRs on treatment among those with ADRs (p=0.01).
Conclusion: ADRs of varying severity are common in patients of MDR-TB on DOTS-PLUS regimen, occurring in more than half of the cases, with around one fifth requiring change of MDR-TB treatment.

Keywords: MDR-TB, ADRs, DOTS-PLUS

INTRODUCTION

The term adverse drug reaction (ADR) has been defined as 'any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug.[1] Adverse reaction to drugs is the most common cause of iatrogenic disease. Any drug, no matter how trivial its therapeutic actions, has the potential to do harm. Incidence of ADR in Indians population is estimated to be 1.75% to 25.1%. Annual estimates of the proportion of outpatients with an adverse drug event range from 5% to 35%.[2,3]

ADRs in hospital in-patients can be divided into two categories: ADRs responsible for hospital admission and those that occur after hospital admission. ADRs were responsible for 3-7% of hospital admissions and these

reactions account for five to nine percent of hospital costs.[4] The incidence of serious ADRs is 6.7% and of fatal ADRs is 0.32% in hospitalized patients.[5]

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB caused by organisms that are resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs.[6] MDR-TB has become a major problem world-wide. According to the reports of world health organization, 3.5% of new TB cases and 20.5% of previously treated cases are estimated to have MDR-TB in the world.[7] India along with China and Russian federation contributes to about half the load of MDR-TB cases.[7]

Drug resistant tuberculosis has frequently been encountered in India and its presence has been known virtually from the time anti-tuberculosis drugs were introduced for the treatment of TB. The national tuberculosis elimination program (NTEP) has recently undertaken three community-based state level drug resistance surveillance (DRS) studies in Gujarat, Maharashtra and Andhra Pradesh. These surveys have been conducted as per a common generic protocol based on internationally accepted methodology and have estimated the prevalence of MDR-TB to be about 3% in new cases and 12-17% in re-treatment cases.[8]

WHO has estimated that in 2009, nearly 99,000 cases of MDR TB emerged in India including those outside NTEP. Among these 64,000 were estimated to have emerged from TB cases notified to NTEP. If left undiagnosed or poorly treated, MDR-TB patients often live and suffer for months to years before succumbing to the disease; hence transmission of MDR can continue, amplifying MDR in the community.[9]

After successfully establishing the DOTS services across the country in 2006, NTEP introduced the programmatic management of drug resistant TB (PMDT) services in India since 2007 to address the needs of MDR-TB patients and is now rapidly scaling up services across the country while also expanding services towards universal access. A standardized Cat IV regimen has been implemented by the NTEP.[9] NTEP has plans to treat about 160,000 MDR-TB and 4,100 XDR-TB cases over the period from 2012-2017.

The duration of MDR-TB treatment is 24-27 months and multiple drugs are used in the regimen which has a great potential for adverse drug reactions. For PMDT to be successful, prompt identification and management of adverse drug reactions is of paramount importance. ADRs are inevitable consequences of multidrug-resistant tuberculosis drug therapy. Reporting of ADR in India is poor and inadequate. ADRs monitoring forms an integral part of pharmacovigilance. ADRs with second line ATT have been mentioned as obstacles in the management of MDR-TB. Compared with the standard 6 months treatment of first-line anti-TB drugs, medications for MDR TB are more complex, combining multiple first-line and second-line drugs for about 24 months, which are less potent, much more expensive and more toxic.[7] Due to long duration of therapy and concurrent use of multiple second-line drugs, ADRs are regarded as the most important clinical consideration in patients undergoing MDR-TB treatment.[10]

These range from mild ADRs (such as nausea/vomiting, headache) to life-threatening ADRs (such as renal failure, hepatotoxicity), which may lead to temporary interruption or permanent discontinuation of chemotherapy.[20] Therefore, it is important for physicians to promptly recognize ADR to second line ATT and manage them, otherwise there will be failure of treatment. This approach ensures better compliance of patients and good treatment outcome.

So, the current study was designed to study the frequency and type of adverse drug reactions related to MDR-TB therapy

METHODS

A prospective observational study carried out at MDR-TB patients of NTEP centre, KIMS Hubli and out-patients and in-patients of medicine and pulmonology department at KIMS Hubli on 72 patients diagnosed as MDR-TB and enrolled for DOTS-PLUS (CAT.IV) regimen at NTEP centre, KIMS Hubli during a period of 1 year study (January 2015 to December 2015). All patients were followed up for a period of 9 months from the day of commencement of treatment.

Inclusion criteria

Individuals aged 18 years and above diagnosed as cases of MDR-TB (confirmed based on drug susceptibility tests) were included in the study.

Exclusion criteria

Pregnant women and individuals less than 18 years of age, HIV positive individuals, patients having concurrent major cardiac, renal, hepatic and/or psychiatric illness, patients with XDR-TB, defaulters of treatment, those who failed to visit regularly (loss to follow up) were excluded from the study.

Ethical considerations

Institution ethics committee permission was obtained. Informed consent was taken from all study participants. All ADRs were managed as per standard NTEP guidelines

Pre-treatment investigations included CBC, LFTs, RFTs, Thyroid function tests, psychiatric screening, FBS, PPBS, chest X-ray, HIV/HBs Ag, urine routine and UPT for all women in the child bearing age group.

Adverse drug reactions were determined by monthly clinical and biochemical monitoring of patients.

In symptomatic and patients with suspected toxicity, required tests and relevant references from other specialties were sought as needed.

Diagnosis of ADRs

ADRs were diagnosed by a combination of direct observation, laboratory report and participant's reports as recommended by the international conference on harmonization (ICH).[11]

For adverse drug reactions defined by laboratory values, at least one documented abnormal value was considered. For those not defined by laboratory values, event was considered if the chest physician/ pharmacovigilance team documented the reaction in any patient according to his/her clinical criteria. Refer table below for definitions of various ADRs.[12]

Statistical analysis

The data was analyzed by frequencies and percentages using SPSS 21.0. Continuous variables were expressed as mean±SD whereas categorical variables were expressed in absolute numbers or percentages. Chi-square test was used to compare and find association between variables. Data was described in the form of tables and graphs. P values less than 0.05 were considered as statistically significant.

RESULTS

In the present study, 72 patients diagnosed as MDR-TB were included in the study and observed for ADRs to Cat IV ATT during the study period. Among these, 42 were males and 30 were females. Of the 72 patients, 44 (61.1%) patients had experienced at least one type of ADRs; comprising 26 male patients and 18 female patients.

Among 72 study subjects, 42 (58.3%) were males and 30 (41.7%) were females. Out of 72 patients, 29 were from 18 to 30 years of age, 29 were 31-45 years of age, 11 were 46-60 years of age and 3 were above 60 years. Mean age of the study sample was 35.86±12.62. Out of 72 patients, 2 (2.8%) were in 16-25 kg weight band, majority i.e., 49 (68.1%) were in 26-45 kg weight band, 21 (29.1%) were in 46-70 kg weight band and none >70 kg category. Mean weight of the study sample was 42.00±9.05 as shown in the Table 1.

Table 1: Demographic profile of the study population.

Parameters	Subgroup	Frequency	Percentage (%)
Sex	Male	42	58.3
	Female	30	41.7
Age (years)	18-30	29	40.3
	31-45	29	40.3
	46-60	11	15.3
	>60	3	4.1
Weight bands (kg)	16-25	02	2.8
	26-45	49	68.1
	46-70	21	29.1
	>70	00	0.0

Table 2: Frequency of adverse drug reactions.

Variables		Frequency	Percentage (%)
ADRs	Yes	44	61.1
	No	28	38.9
Number of ADRs	One	18	41
	Two	13	29.5
	Three	11	25.0
	Four	02	4.5

Of the 72 patients, 44 (61.1%) patients had experienced at least one type of ADRs; and no ADRs were seen in 28 (38.9%) patients. Out of 44 patients who showed ADRs, 18 patients had only one ADR, in 13 patients two ADRs, in 11 patients three ADRs and in 2 patients four ADRs were seen. A total of 85 ADRs were seen in 44 patients who showed ADRs (Table 2).

Table 3: Association of various factors with ADRs.

Factors		ADRs		Chi square	P value
Gender	Male	26 (61.9)	16 (38.1)	0.0066	0.934
	Female	18 (60.0)	12 (40.0)		
Weight bands (kg)	16-25	02 (100)	0 (0)	1.87	0.393
	26-45	28 (57.1)	21 (42.9)		
	46-70	14 (66.7)	07 (33.3)		
Age (years)	18-30	18 (62.1)	11 (37.9)	0.2609	0.9672
	31-45	18 (62.1)	11 (37.9)		
	46-60	6 (54.5)	5 (45.5)		
	>60	2 (66.7)	1 (33.3)		
Smokers	Yes	14 (66.7)	07 (33.3)	0.126	0.723
	No	30 (58.5)	21 (41.2)		
Alcoholic	Yes	13 (72.2)	05 (27.8)	0.701	0.402
	No	31 (57.4)	23 (42.6)		

An attempt was made to study the association of various factors like gender, weight bands, age, smoking and alcohol with ADRs but no factor was found to be significantly associated with it (p=0.05) (Table 3).

Table 4: Frequency of individual ADRs noted during treatment of MDR-TB patients.

ADRs	Frequency (no. of pts with ADRs)	Percentage (%)
GIT	21	29.2
Anorexia	11	15.3
Giddiness	9	12.5
Pain at injection site	8	11.1
Arthralgia	7	9.7
G. B. A	7	9.7
Headache	6	8.3
Ototoxicity	3	4.2
Peripheral neuropathy	3	4.2
Pruritis	3	4.2
Visual disturbances	1	1.4
Nephrotoxicity	1	1.4
Hepatotoxicity	1	1.4
Psychiatric manifestations	1	1.4
Skin Rash	1	1.4

In our study ADRs were seen in 44 patients with GIT symptoms, anorexia and giddiness as the three most common ADRs (Table 4).

Table 5: Association between ADRs with change of treatment.

ADRs	Treatment changed (%)	Treatment unchanged (%)	Total (%)	P
ADRs present	09 (20.5)	35 (79.5)	44 (100)	0.01
ADRs absent	00 (0)	28 (100)	28 (100)	
Total	09	63	72	

P<0.05 of significant impact of ADRs on change of treatment among those with ADRs (Table 5).

DISCUSSION

In our study, out of 72 patients, 44 (61.1%) patients had experienced at least one type of ADRs. Many other studies also reported a similar incidence. In a systematic review and meta-analysis by Shanshan et al, 2602 out of 5346 patients had at least 1 kind of ADR (57.3%).[13] In a retrospective study by Baghaei et al, 45 out of 80 patients developed ADRs (56.3%).[10] While in study done by Rohan et al, 55 out of 110 patients developed at least 1 kind of ADRs (50%).[14] In a study by Torun et al 182 out of 263 cases developed at least one or more ADR (69.2%).[15]

Among 72 patients included in the study, 42 (58.3%) were males and 30 (41.7%) were females. In study by Avong et al, 62% were males and 38% were females.[16] There was no statistically significant difference noted in the occurrence of ADRs among males or females. In 2013; the male: female ratio of notified cases across all age groups was 1.6 globally.[17] This has been explained both by socio-cultural factors, thus run a greater risk of exposure to contagious cases, and by immunological differences between men and women that make males more susceptible than females to some infections.[18,19]

Out of 72 patients, 29 were from 18 to 30 years of age, 29 were 31-45 years of age, 11 were 46-60 years of age and 3 were above 60 years. Mean age of the study sample was 35.86±12.62. This age represents the period of physical, mental and occupational stress. This is consistent with various other studies carried out by Sagwa et al (mean age 34.7 years), Isaakidis et al (mean age 35.5 years).[20,21]

The association between the occurrence of ADRs in various age groups was not statistically significant, although ADRs were more common in elderly aged >60 years (66.7%) than in other age groups. As people age, the capacity of liver to metabolize many drugs becomes less and also the renal function to eliminate drugs from the body declines. These age-related problems are often made worse by malnourishment and dehydration, which tend to become more common as people age.[22] Similarly the occurrence of ADRs among smokers and non-smokers, alcoholics and non-alcoholics was found to be statistically insignificant.

Malnutrition is a major health problem in developing countries like India which leads to poor immunity and so associated with adverse outcomes. Although ADRs were most commonly seen in lowest weight band i.e., 16-25 kg, the occurrence of ADRs across various weight bands was statistically insignificant in our study. Study done by Vishaka et al showed poorer treatment outcomes in malnourished patients.[23]

In the present study a total of 85 ADRs were seen in 44 patients with GIT symptoms, anorexia, giddiness and pain at the injection site as the four most common ADRs. GIT symptoms (29.2%) were most common adverse reactions in our study similar to various other studies.[13,14] More serious events, such as psychiatric episodes (1.4%), hepatotoxicity (1.4%) nephrotoxicity (1.4%) and visual loss (1.4%), were relatively less frequent.

In a study done by Rohan et al, the four MC ADRs were G.I.T symptoms (30%), arthralgia (4.5%) psychosis (4.5%) and hepatotoxicity (3.6%).[14] In study done by Shanshan et al, the four MC ADRs were gastrointestinal disorders (32.1%), ototoxicity (14.6%), psychiatric disorders (13.2%) and arthralgia (8.1%).[13]

Similar to studies of patients on MDR-TB treatment in India and the United States adverse events were more common during the first 6 months of treatment.[24] Injectable MDR-TB medications, which are often given only during the first 6-9 months of treatment may account for the higher incidence during this time period. Frequent monitoring and prompt intervention during the early months of treatment should be a fundamental part of MDR-TB management.[25] In present study, ADRs were most common during first 3 months of initiation of MDR-TB therapy accounting for nearly 61.4% of ADRs followed by 29.5% during 4-6-month period and 9.1% during 7-9-month period. Similarly, in study by Avong et al majority of ADRs developed after 1-2 months of therapy, and resolved in less than a month after treatment.[16] Isaakidis et al reported that most of the adverse effects occurred between 2nd and 4th month of MDR-TB treatment initiation.[21]

In present study 9 out of 72 patients (12.5%) required change of treatment and discontinuation of the incriminating agent {i.e., 20.5% of 44 patients who developed ADRs required change in treatment}. This was comparable to study from Lima, Peru which reported 11.7% required discontinuation of the offending drug. [26] Similarly in study by Baghaei et al, 56.3% (45/80) of patients developed ADRs, of whom 21.2% required the discontinuation of the incriminating drug.[10] While in study done by Nathanson et al, the results show that among 818 patients enrolled on MDR-TB, 30% required removal of the suspected drug(s) from the regimen due to ADRs.[23] In a retrospective case series by Shin et al, out of 244 MDR-TB patients, 70 patients (28.7%) required permanent discontinuation of an offending agent due to ADRs.[12]

Only 9 out of 44 patients who showed ADRs required change in their treatment part. Most of the other ADRs were managed on OPD basis with the use of ancillary medicines. None of the patients required termination of the entire MDR-TB regimen due to adverse reaction alone which is consistent with studies done by Shin et al and Furin et al.[12,26] Two out of 7 arthralgia cases and two out of 3 ototoxicity cases required change in their treatment schedule. One case of ototoxicity (hearing loss) was reported during 7th month and patient was already off kanamycin. Therefore, patient was asked to come for regular follow up with the ENT specialist and treatment was not changed.

While one case each of nephrotoxicity, hepatotoxicity, skin rash, psychiatric disturbances (psychosis) and visual loss was reported during the study and all required change in the treatment schedule. The suspected drug/s was stopped and reserve drug PAS was used where ever feasible. Patient with skin rash had no mucosal involvement and involved <10% of B.S.A. which was controlled with anti-histaminic and emollients. FQs and pyrazinamide were withheld till rash subsided and were re-introduced later on consultation with the specialist.

Limitations

Finally, there may be potential reporting bias as some type of ADRs was reported by patients subjectively, such as nausea, vomiting, and numbness. Further limitation was the fact that the few ADRs were recorded based on clinical assessments that were made by the treating doctors particularly those for which laboratory criteria were not used. Therefore, to some degree, they were subjective too. However, reporting in this manner is in accordance with WHO tuberculosis and DOTS plus treatment guidelines. Another difficulty in recording ADRs is determining if the effect is due to the TB medication or the TB disease itself, which is why any symptoms present before treatment were not included.

CONCLUSION

The treatment of MDR-TB is prolonged, expensive, more toxic and often unsuccessful. Hence, prevention of MDR-TB is more important rather than treatment. Strengthening the program by intensely evaluating treatment regimens, assuring treatment adherence, aggressive and proactive management of adverse events and infection control are very essential to improve outcome in MDR-TB. Efforts should be made to continue treatment in the face of adverse effects as long as they fall short of being life threatening. The timely and aggressive management of adverse effects is therefore important to keep patients in treatment in the follow-up of MDR-TB cases.

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