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Original Research Article

A Study of Adverse Drug Reactions Caused by Second Line Anti-Tubercular Drugs Used in Nepal

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ABSTRACT

Background: The aim of the study was to investigate the pattern of adverse drug reactions caused by second line anti-tubercular drugs used in Nepal.
Materials and Methods: The study was carried out in Directly Observed Treatment Short Course Plus (DOTS PLUS) Centers and Sub-Centers all over Nepal. All the patients under Multi Drugs Resistance Tuberculosis (MDR-TB) treatment were studied. The medication files of the patients who were taking medicines from these centers were taken. Further analysis were done using Microsoft excel 2007 spreadsheet along with Naranjo Algorithm for causality assessment and Modified Hartwig and Siegel scale for determining severity.
Results: Total MDR patients (366) under MDR-TB treatment in Nepal through DOTS PLUS were studied, in which 14 were Human Immunodeficiency Virus (HIV) positive and excluded and on remaining, 68 (19.32%) patients developed at least one ADR. Total 140 ADRs were detected in this study. Average onset time of ADRs was 7.85 months. The most common ADR was joint pain/arthralgia experienced by 26 (38.34%) patients. It was found that 49 (35%) ADRs were 'probably' and 91 (65%) were 'possible' due to the suspected drugs. Ofloxacin accounted for 92 (35.94%) of the ADRs. More than half i.e. 59 (86.77%) patients developed mild ADRs.
Conclusion: Anti-tuberculosis drugs for MDR-TB treatment could cause ADRs both in quantity and severity. Male had a higher incidence of ADRs. Majority of the ADRs were 'mild' and had a 'possible' relationship with the suspected drugs.

Keywords: Adverse drug reaction, Multi drug resistance, Multi drug therapy, Nepal, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) an infectious disease caused by *Mycobacterium tuberculosis*, has now become the second leading infectious cause of death in the world. [1] It has been reported by WHO that one third of the world's population is infected with Mycobacterium tuberculosis resulting in 8.4 million new tuberculosis cases in 1999. [2] The World Health Organization (WHO) declared tuberculosis (TB) as a global emergency in 1993. [3] In Nepal, it is considered to be a dangerous disease and estimates suggest nearly 45 deaths per day are due to TB (National Tuberculosis Centre, 2000). In Nepal, about 60% of the economically productive population has been infected with TB. Over 80,000 people in Nepal have TB, about 40,000 people develop TB every year and nearly half of them have infectious sputum positive TB and can

transmit the disease to others. Despite the development of modern health care services across the country, many people in Nepal still do not have access to effective TB treatment. An estimated 5,000- 7,000 people continue to be died of TB every year in Nepal. [4] One of the reasons for such high mortality could be non-compliance to treatment. [5] Adverse drug reactions (ADRs) can be a potential factor leading to treatment non-compliance. Studies from different parts of world suggest that more than 5% of the patients on anti-tubercular treatment (ATT) develop ADRs. [6-8] All antitubercular drugs can cause adverse drug reactions and may result in ADRs involving almost all systems in the body, including the gastrointestinal tract, liver, skin, nervous system, oto-vestibular apparatus and the eyes. [9] There are common ADRs observed in DOTS therapy such as mild gastritis, central nervous system, peripheral nervous system, liver, psychiatric, dermatologic, musculoskeletal, renal, otologic, ocular, hypothyroidism, icterus, fever, breathing disorder. [10-12] Numerous clinical trials have determined that there is a 15% probability of an adverse effect occurring in a patient who is on a multiple antitubercular drug regimen and adverse reactions mostly tend to occur in the first three months of treatment. [13]

Studies have found that ADRs account for 5% of all hospital admissions and cause death in 0.1% of medical and 0.01% of surgical cases. [14] It has been found that 50% of the ADRs are preventable in the initial place. [15] Worldwide, many countries have started ADR monitoring programs with varying degree of success. In Nepal, however, ADR monitoring is still a new concept. The national drug controlling authority of Nepal, Department of Drug Administration (DDA), has recently taken steps to establish an ADR monitoring program in Nepal. [16] The first step taken for TB Control was in 1937 with the establishment of 'Tokha Sanatorium' situated on the north of Kathmandu city. Secondly, the Central Chest Clinic (CCC) came into existence in 1951 with the facility of Diagnosis and Treatment services for the TB patients on domiciliary basis. Simultaneously, Nepal Anti-TB Association (NATA) was established in 1953 and initiated its TB Control services with opening of outpatient Clinic in 1955 and established a Chest Hospital in 1970. [17]

Manipal Teaching Hospital (MTH), a tertiary care teaching hospital in Pokhara, Western Nepal, has started spontaneous reporting program at the hospital level since September 2004. [18] Some other study found that Anti-TB drugs could cause significant adverse effects both in quantity and severity. These reactions may lead to hospitalization, prolonged hospital stay and even death. It is found that Asian People may develop more frequently severe adverse reactions, such as hepatitis, induced by this class of medicines. [19] It indicates that the protocol of Anti-TB therapy for Asian population may need some revision to prevent fatal hepatotoxicity.

Identification of the ADR profile of drugs can be useful for the prevention, early detection and management of ADRs. Identifying the causality and severity assessments of ADRs is an important step in ADR monitoring programs. Naranjo's Algorithm [20] and the WHO Probability Scales [21] are commonly used to carry out the assessment of the causality of the ADRs. Similarly, the Hartwig *et al* Scale [22] is a commonly used scale for identifying the severity of ADRs.

Detailed information regarding the safety profile of ATT drugs are lacking in Nepal. Moreover, identifying the pattern of ADRs due to ATT drugs can provide valuable information for the prescribers and the policy makers in implementing appropriate measures in preventing the

occurrence of similar ADRs. Hence we conducted the study with the following objectives.

1. To study the pattern of adverse drug reactions in the patients with different demographic groups.
2. To determine severity of adverse drug reactions.
3. To establish the casual relationship between the drug administration and adverse events.
4. To determine suspected drugs associated with adverse drug reactions.
5. To determine the onset time of adverse drug reactions.

MATERIALS AND METHODS

The materials and methods of the study are as follows:

***Study type*:** A prospective cross-sectional study

***Study Site*:** The study was carried out at medication units in DOTS PLUS Centers and Sub-Centers, Nepal. There are 11 DOTS PLUS treatment centers in Nepal, i.e. 2 in eastern region, 3 in central region, 3 in western region, 1 in mid-western region and 2 in far-western region.

Inclusion and exclusion criteria: All the patients who were under MDR-TB treatment in all DOTS PLUS Centers and Sub-Centers were enrolled in the study. Among them all ADR cases were further studied. Patients having other associated diseased condition and receiving drugs (like HIV, Diabetes, Pregnancy, Renal failure, steroids, etc) are excluded. It was done to determine sole ADRS associated with MDR-TB treatment drugs.

***Sample size*:** Patients taking MDR-TB treatment drugs under DOTS PLUS program all over the nation were taken during the study period.

***Tools used*:** Patient ADR Documentation form was used as a data collection tool to gather data from patient medication record. The patient medication record for MDR-TB patient includes various forms as below:

- Tuberculosis treatment card
- Side effect recording form
- Sputum examination request form

As a compiled and modified form, patient ADR documentation form was prepared.

***Operation modality*:** The patient's medication card along with adverse drug reaction reporting card was studied and the cases of ADR were noted down. Overall data collection was authenticated along with the permission and approval of Director, Nepal Tuberculosis Center. The reported ADR of the patients taking medicine till the date were considered. After ADR reports were collected, all the necessary information was filled on Patient ADR Documentation Form. Data of all MDR-TB patients were observed, whereas only the data of ADR cases were collected and analyzed using standard scales.

***Result analysis*:** Results were analyzed using Microsoft excel 2007 spreadsheet. Firstly, data were entered in spreadsheet in various heading. Total counting, mean and standard deviation were determined by using formula in same sheet. Data were expressed through bar charts and tables. For severity of ADRs Modified Hartwig & Siegel method was used. Similarly for causality of ADRs Naranjo Scale was used.

RESULTS

Total registered MDR-TB patients in Nepal were 816. All together 366 patients in whole Nepal were under MDR-TB treatment, among them 14 were HIV infected which were excluded in our study. Among the remaining patients 68 developed at least one ADR giving an incidence of 19.32%.

***Sex distribution*:** Among the 68 (100%) patients affected with ADR 56 (82.35%) were male and 12 (17.65%) were female.

***Age distribution*:** More numbers of patients were within the age group 31- 40 years. The mean ± SD of the age of the

patients was 39.57 ± 13.93 years. The details regarding the age distribution of the patient are listed in Table 1

Ethnic distribution: More number of patients were Chhetri (16.18%) followed by Brahman (14.71%) and Tamang (11.76%).

Weight distribution: More numbers of patients were within the weight group 36-50 kg. The mean ± SD of the age of the patients was 50.04 ± 9.63 kg. The details regarding the weight distribution of the patient are listed in Table 1.

Table 1: Demography distribution of the patients with ADRs caused by second line anti-tuberculer drugs

Parameters		Number	Percentage
Sex	Male	56	82.35
	Female	12	17.65
Age (in years)	Up to 20	6	8.82
	21-30	14	20.59
	31-40	19	27.95
	41-50	16	23.53
	51-60	5	7.35
	More than 60	8	11.76
Body weight (in Kgs)	Below 24	0	0
	25-35	4	5.88
	36-50	31	45.59
	51-65	27	39.71
	66 above	6	8.82
Ethnic group	Brahmin	10	14.71
	Chhhetri	11	16.18
	Tamang	8	11.76
	Newar	6	8.82
	Lama	6	8.82
	Sherpa	5	7.35
	Magar	5	7.35
	Thapa	5	7.35
	Gurung	4	5.90
	Bikram Kami	2	2.94
	Others	6	8.82

Table 2: Various type of ADRs (n = 140)

Types of ADR	**Reported Number of ADR**	**Percentage**
Nausea/vomiting/anorexia	24	17.14
Joint Pain/arthralgia	26	18.57
Vertigo/ dizziness	23	16.43
Weakness/body ache	5	3.57
Epigastric pain/burning	1	0.71
Shortness of breath	1	0.71
Anemia	8	5.71
Hearing loss	10	7.14
Vision loss	8	5.71
Insomnia/minor mood change	11	7.86
Depression	4	2.86
Diarrhea	4	2.86
Psychosis	6	4.29
Edema/itchy skin	5	3.57
Hair loss	1	0.71
Hypothyrodism	3	2.14
Total	**140**	**100**

***Types of ADRs affecting the patients on multi drug resistance tuberculosis treatment*:** Altogether, 140 ADRs were experienced and details are listed in Table 6. Majority of the ADRs were related to the Joint pain/Arthralgia 26 (18.57%) followed by Nausea/Vomiting/Anorexia 24 (17.14%), Vertigo/Dizziness 23 (16.43%). Maximum number of ADR in a person was found to be 8. The mean ± SD ADR per person was 2.06±1.41.

***Onset time (Months) of adverse drug reactions*:** Most of the ADRs were observed within 5 months. The mean ± SD onset time was 7.85 ± 5.56 months.

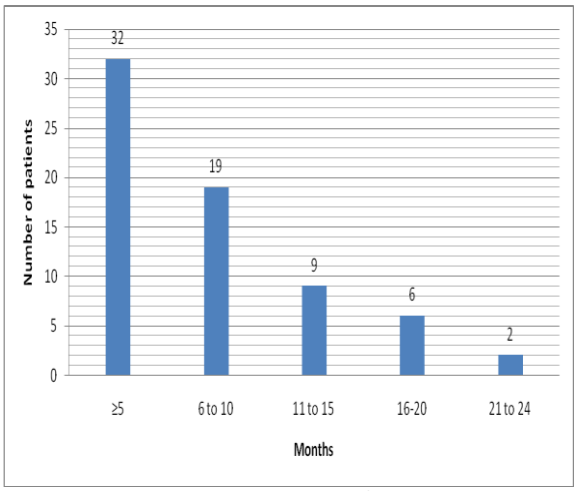

Figure 1: Onset months of ADRs

Suspected drugs: All the drugs used for MDR-TB treatment were suspected as our result. Maximum numbers of ADRs were due to Ofloxacin. Ethionamide, Cycloserine, Kanamycin and Pyrazinamide are also suspected in descending order.

Table 3: Suspected drugs causing the ADRs on MDR-TB Treatment (n = 256)

Suspected Medicines	No. of ADR Developed	Percentage
Ofloxacin	92	35.94
Ethionamide	56	21.88
Cycloserine	44	17.19
Kanamycin	33	12.89
Pyrazinamide	31	12.10

Causality assessment (Naranjo algorithm): Out of 140 ADRs occurred in MDR-TB under treatment patients 49 (35%) were probable and 91 (65%) possible due to the suspected drugs.

Severity of adverse drug reactions: Severity according to modified Hartwig & Siegel scale includes seven levels which are classified under mild, moderate and severe. In our study 59 (86.77%) were found to be mild [level (1)] as the major. None of the patients experienced severe ADRs.

Table 4: Severity of ADRs on MDR-TB under treatment patients

Severity	No. of Patients	Percentage
Mild [Level (1)]	59	86.77
Moderate [Level (3)]	8	11.76
Moderate [Level (4)]	1	1.47

Life threatening ADR was not observed in this study although 6 (8.82%) out of 68 had to discontinue the medication due to many ADRs like anemia, peripheral nervous system effects and arthralgia. But the drugs were withdrawn only for two weeks and then again reintroduced. Likewise, 2 (2.9%) out of 68 had received alter dose of Cycloserine due to severe peripheral nervous system disorder and psychiatric symptoms.

DISCUSSION

These data are the first available evidence of prevalence of ADR associated with the use of second line drugs within the context of DOTS-Plus project of NTP, Nepal. We had expected that the occurrence of life-threatening ADR would be higher than reported in the literature in light of the long anti-tuberculosis treatment history and extensive use of toxic second-line drugs. But life-threatening ADR was not observed in this study. Furthermore, discontinuation of drugs was observed only within few patients (8.82%) which is very less as compared to previous studies. In one landmark study on the treatment of MDR TB, Goble and colleagues reported that 30% of patients had adverse effects requiring discontinuation of one or more anti-tuberculosis medications. [23] Similarly, in a study from India, 40% patients experienced side effects, defined as those requiring either no discontinuation of a drug or discontinuation for <1 week and manageable at peripheral level. [24]

When MDR-TB is suspected on the basis of history or epidemiological information, the patient's sputum must be subjected to culture and anti-tuberculosis drug sensitivity testing and the WHO re-treatment regimen [25] or the empirical regimens employing second-line reserve drugs suggested by the American Thoracic Society [26] must be initiated pending sputum culture report. Further therapy is guided by the culture and sensitivity report. In a study from Peru on occurrence of ADRs in patients receiving therapy for MDR-TB, patients received a median of 8.0 (5–12) anti-tuberculosis drugs. [10] In our study all patients received all five drugs as empirical regimens with varying doses according to their weight. This might be the reason that life-threatening ADRs were not observed and discontinuation of drug was also less.

Females are at higher risk of developing ADRs as they pass through different life stages like pregnancy, menarche etc. but in our study out of 68 patients with ADR, 82.35% were male showing higher incidence of ADR. This is because of higher cases of MDR-TB in male than female in Nepal.

Elderly are more prone to the ADRs because of reduced liver, kidney and other systemic function as a consequences of increased age. In this study higher proportion of ADRs were observed in the age groups ranges from 20-50. Within the same age ranges similar proportion of ADRs were observed in a study on pattern of adverse drug reactions experienced by tuberculosis patients in a tertiary care teaching hospital in western Nepal [27] which was the study on the first line drugs.

In this study the most common ADR observed was arthralgia and second common was gastrointestinal problem. In a study from India on the results of DOTS-

Plus program, gastrointestinal effects (40%) occurred as major ADR [24] with the commonest symptoms being nausea and vomiting. Likewise, similar observations were made when data on adverse events were collected from five DOTS-Plus sites in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast). The five most common adverse events were nausea/vomiting (32.8%), diarrhea (21.1%), arthralgia (16.4%), dizziness/ vertigo (14.3%) and hearing disturbances (12%). [28] In our study dermatological effect that includes itchy skin occurred in only 3.75 % while in different studies this condition has been reported to occur in higher proportion, as many as 30%. [10]

Occurrence of peripheral nervous system effects was also found to be high. 23 (16.43%) patients developed vertigo/ dizziness, 11(7.86%) developed mood change behaviour, 4(2.86%) developed depression and 6(4.29%) developed psychosis. In a study from Peru on psychiatric issues in the management of patients with multidrug-resistant tuberculosis, 12% patients developed mood change behaviour, 13.3% developed depression and 12% developed psychosis. [29] It should be noted that in this study all the patients had received previous regimens with at least one neurotoxic drug like Isoniazid and Streptomycin. Furthermore, all had received high dose of pyridoxine so as to minimize this effects. Still there were 2 (2.29%) patients in whom dose of Cycloserine was decreased due to neuropathic disorder with symptoms like psychiatric symptoms, psychosis, minor mood change and depression. Moreover, 6 (8.2%) patients had to withdraw Cycloserine for up to two weeks due to increased neuropathic disorder. Not only the pyridoxine but Ranitidine was also given to all patients throughout the therapy so as to minimize the gastric problems but still these problems were observed as second most common ADRs with associated symptoms as nausea, vomiting, anorexia etc.

It is very important to identify the drugs which are responsible for causing ADRs. This will help to prevent and manage the ADRs. In this study Ofloxacin, Ethionamide and Cycloserine were the major drugs responsible for causing ADRs. Ofloxacin and Ethionamide were responsible for causing minor ADRs in higher frequencies whereas Cycloserine was responsible for causing few ADRs of moderate one due to which withdrawing or dose alteration was done. Furthermore, onset of ADRs is also important for the early detection of ADRs. In this study most of ADRs were observed after 5 months of initiation of medication. In a study from Peru on occurrence of ADRs in patients receiving therapy for MDR-TB, patients with ADRs had given medications for at least 6 months. [10]

Naranjo algorithm is widely used in carrying out the casualty assessment. [20] In our study this algorithm was used to establish the casual relationship between the drug administration and adverse events. We found 65% of ADRs had 'possible' relationship whereas 35% of ADRs had 'probable' relationship with the use of suspected drugs. Similarly assessment of severity of ADRs is also important for the management of ADRs. For this purpose, Hartwig scale [21] is widely used. This scale categorizes the reported adverse drug reactions into different levels as mild, moderate or severe. We found 59 patients with mild ADRs and 9 patients with moderate ADRs.

CONCLUSION

In conclusion, this study is able to identify the pattern of ADRs caused by second line anti-tubercular drugs used in Nepal. Anti-tubercular drugs for MDR-TB treatment could cause significant ADRs both in quantity and severity. Male had a higher incidence of ADRs. Majority of the ADRs were 'mild' and had a 'possible'

relationship with the suspected drugs. More than half of ADRs were observed within 5 months of treatment. Since, there is very less number of researches on this issue, our research is the first in Nepal. Further, more studies should be carried out to diagnose more fact about this. This will create the tackling ideas and frequent revision of medication system in TB.

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