PATTERN OF ADVERSE DRUG REACTIONS EXPERIENCED BY TUBERCULOSIS PATIENTS IN A TERTIARY CARE TEACHING HOSPITAL IN WESTERN NEPAL

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ABSTRACT

Tuberculosis is a common problem in developing countries including Nepal. Data regarding the safety profile of anti tubercular drugs is lacking in Nepal. The present study analyzed the pattern of ADRs caused by the antitubercular drugs. Inpatient files of all the TB patients who received treatment at the Manipal Teaching Hospital, Pokhara, Nepal during the period from 1st January 2001 till 31st December 2006 were taken. Altogether 326 patients were identified among which 40 (females 24, males 16) experienced at least one ADR (incidence 12.27%). The mean ± SD age of the patients was 42.12 ± 20.41 years. The most common ADR was elevated liver enzymes [24 (57.14%)] and hepatobiliary system was the most common system affected [24 (58.5%)]. More than half the ADRs [21 (52.55%)] developed with in 20 days of initiation of therapy. Isoniazid and pyrazinamide were the suspected drugs responsible for 32.32% each of the total ADRs. The mean ± SD of the total number of drugs used in the patients were 4.77 ± 1.46. The most common laboratory abnormality observed was elevated SGOT level [21 patients (52.5%)]. Seven (17.5%) patients needed specific drug treatment for managing the ADRs and 10 (25%) needed symptomatic management. Thirty five (87.5%) patients recovered following the ADR. Multiple drug therapy was the reason behind the development of 30 (75%) ADRs. It was found that 29 (72.5%) ADRs were 'probably' due to the suspected drugs. Majority [19 (47.5%)] of the ADRs were mild [level (1)]. This study shows that ADRs to anti tubercular drugs are common. Since TB is a common problem in Nepal, special efforts are needed to tackle the drug related complications associated with ATT drugs.

Keywords: Adverse drug reactions, anti tubercular treatment, Nepal, tuberculosis.

INTRODUCTION

Tuberculosis (TB) is one of the common problems worldwide, affecting eight million new people and causing two million deaths every year (Nehaul, 2003). 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). The magnitude of the problem is further worsened by the recent epidemic of HIV/AIDS. In order to reduce the burden of TB in Nepal, the government has taken several strategies. A major strategy is the establishment of Directly Observed Treatment Short course (DOTS) centers (National Tuberculosis Centre, 2000). However, TB is still a threat in Nepal (Harries *et al*., 1998). The most recent report estimates that from 5000 to 7000 people in the country died in 2002/2003 due to TB (National Tuberculosis Centre, 2004). One of the reasons for such an outcome could be non-compliance to treatment (Van der werf *et al*., 1990). 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 (Ormerod and Horsfield, 1996; Dhingra *et al*., 2004 and Chukanov *et al*., 2004). Some of the ADRs can be even fatal. One study from the central part of Nepal had reported the pattern of heptotoxicity due to ATT drugs (Shakya and Rao, 2004). Another multi-centre study conducted in five hospitals in Nepal identified that 15.87% of the drug related complications were due to ATT drugs (Shrestha *et al*., 2006). One study from Western Nepal studied the ADRs occurring during DOTS therapy and assessed their causality, severity and predisposing factors. This study was done in the DOTS center and was based on patient interviews. Many useful parameters were however not available (Anupa, 2006). 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.

Objectives

The objectives of the study are as follows:

1. To study the demographic and ethnic details of the patients experiencing ADRs
2. To study the pattern of ADRs caused by the antitubercular drugs
3. To study the predisposing factors for developing ADRs and

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4. To carry out the causality and severity assessments of the ADRs.

MATERIALS AND METHODS

The materials and methods of the study are as follows:

Study type: Retrospective study.

Study site: Manipal Teaching Hospital (MTH), Pokhara, Nepal, a 700 bedded tertiary care teaching hospital located in Western Nepal. The hospital also has an attached DOTS center which is maintained under the DOTS program of Nepal.

Inclusion and exclusion criteria: All the patients who developed ADRs which were documented in the files were included in the study. Patients for whom the files were not located and without proper documentation were excluded from the study.

Tools used: A self developed patient profile form was used for the study (Appendix 1)

Operational modality: The files of all the TB patients who received treatment at MTH during the time period from 1st January 2001 till 31st December 2006 were taken up for analysis. The chest physician reviewed the files thoroughly and looked for any documented ADRs. All the patients who developed at least one ADR were noted and the details entered in the patient profile form developed for the study. The filled patient profile forms were analyzed for specific results.

Result analysis: The data obtained from the filled patient profile forms were entered in the Microsoft excel spread sheet and analyzed.

Results: All together 593 patients was registered at the DOTS centre attached to the MTH, out of which only 326 patient records were available and hence were analyzed. Among these patients 40 developed at least one ADR giving an incidence of 12.27%.

Patient demography: The mean ± SD age of the patients developing ADRs was 42.12 ± 20.41 years. The demography and ethnic details of the patients who developed ADRs are listed in table 1.

Table 1: Demography distribution of the patients on ATT affected with ADRs

Parameters		Number	Percentage
Sex	Male	16	40
	Female	24	60
Age (in years)	Up to 20	6	15
	21-30	8	20
	31-40	7	17.5
	41-50	5	12.5
	51-60	5	12.5
	More than 60	9	22.5
Body weight (in Kgs)	Up to 35 Kgs	0	0
	36-45	14	35
	46-55	11	27.5
	56-65	4	10
	66-76	3	7.5
	Above 76	1	2.5
	Details not available	7	17.5
Ethnic group	Bahaun	8	20
	Chhetri	10	25
	Gurung	8	20
	Bikram Kami	2	5
	Lama	2	5
	Magar	2	5
	Shrestha	2	5
	Sunar	1	2.5
	Tamang	1	2.5
	Rana	1	2.5
	Others *	3	7.5

* = The ethnic group of these patients could not be identified from their names.

Table 2: Various type of ADRs affecting the patients on ATT (n=42)

Type of the ADR	No. of reports	Percentage
Elevated hepatic enzymes/ hepatitis	24	57.14
Gastritis	4	9.52
Joint pains	4	9.52
Erythematous/ Macular rash	3	7.14
Interstitial nephritis/ Renal failure	2	4.76
Nausea / Vomiting	2	4.76
Peripheral neuritis	1	2.38
Vestibular neuritis	1	2.38
Defective vision	1	2.38

Note: Some patients might have had more than one ADR

Known allergies: Among the 40 patients who developed ADRs, 2 (5%) had a previous history of drug allergy. We could not locate information about previous drug allergy for the other patients.

Type of ADRs: There were a total of 42 ADRs among the 40 patients studied. The most common was elevated liver enzymes/hepatitis which was observed in 24 (57.14%) patients. The details regarding the various types of ADRs developed by the patients are listed in table 2.

System affected by the ADRs: Hepatobiliary was the most common system affected by the ADRs [24 (57.1%)] followed by GIT [6 (14.3%)], skeletal system [4 (9.5%)], skin [3 (7.1%)], renal [2 (4.8%)], and CNS, Ear and Ocular [one each or 2.4%].

Onset of the ADRs: Among the total of 40 patients, 21 (52.5%) experienced the ADRs with in 20 days, 3 (7.5%) in 21-40 days, 9 (22.5%) with in 41-60 days and the remaining 7 (17.5%) in more than 60 days after starting the treatment.

Suspected drugs causing the ADRs: The various drugs suspected for the development of ADRs are listed in table 3.

Table 3: Suspected drugs causing the ADRs in the patients on ATT (n=99)

Suspected drugs	No. of reports	Percentage
Isoniazid	32	32.32
Pyrazinamide	32	32.32
Rifampicin	31	31.31
Ethambutol	3	3.03
Streptomycin	1	1.01

Number of drugs used in patients: The mean ± SD number of drugs used in the patients were 4.77 ± 1.46. Among the total 40 patients, 4 (10%) had 3 drugs prescribed, 13 (32.5%) had 4 drugs, 6 (15%) had 5 drugs, 9 (22.5%) had 6 drugs and 4 (10%) had more than 6 drugs prescribed at the time of development of the ADR.

Laboratory abnormalities: The most common laboratory abnormality observed in the patients who developed ADRs was elevated Aspartate transaminase (AST) level in [21 (52.5%)] patients, followed by elevated Alanine transaminase (ALT) [18 (45%)], elevated uric acid [5 (12.5%)], elevated Alkaline phosphatase [5 (12.5%)] and elevated serum creatinine in 2 (5%) of the patients. There were no associated laboratory abnormalities for 12 (30%) of the patients.

Management of the ADRs: Among the patients developing the ADRs, 7 (17.5%) needed specific treatment and 10 (25%) needed symptomatic management. Treatment was not needed for 22 (55%) of the patients and the details regarding management of the ADR was not available in the case of 1 (2.5%) patient.

Outcome of the ADRs: Thirty five (87.5%) patients recovered following the ADR and in one patient the ADR was continuing at the time of discharge. The outcome of 3 (7.5%) patients were not available and the details were not available for 1 (2.5%) of the patients.

Dechallenge: Among the 40 patients, dechallenge was done in the case of 10 patients. Among these 8 improved, one did not improve and the status of one patient was unknown.

Rechallenge: Rechallenge was done in the case of 9 patients and symptoms recurred in the case of 2 patients. In 7 cases there was no recurrence of symptoms.

Predisposing factors for ADR: It was found that multiple drug therapy was the reason behind development of 30 (75%) of the ADRs, age in 6 (15%), intercurrent drugs (Pyridoxine was not prescribed) in 1 (2.5%) and the details of 3 (7.5%) patients were not known.

Causality assessment (Naranjo algorithm): It was found that 29 (72.5%) of the ADRs were probably due to the suspected drugs, 8 (20%) possibly and 3 (7.5%) were definitely attributable to the suspected drugs.

Severity assessment: The severity assessment of the ADRs were analyzed and it was found that majority [19 (47.5%)] of the ADRs were of Mild category [level (1)]. The details regarding the severity of the ADRs are listed in table 4.

Table 4: Severity of ADRs according to the severity assessment scale (Modified Hartwig and Siegel)

Dechallenge	No. of patients	Percentage
Mild [level (1)]	19	47.5
Mild [level (2)]	3	7.5
Moderate [level (3)]	5	12.5
Moderate[level (4a)]	8	20
Moderate[level (4b)]	1	2.5
Details not available	4	10

DISCUSSION

Tuberculosis is a highly prevalent disease in Nepal (Harries *et al*, 1998). In spite of implementation of DOTS, it is still a major health concern. Among the various problems associated with TB, the toxicity associated with ATT drugs is a major concern. The present study analyzed the pattern and nature of ADRs due to ATT drugs.

In our study, the incidence of ADRs was 12.27%. Two studies from Russia reported an incidence of 72.8% (Chukanov *et al*, 2004) and 60.2% (Tashpulatova, 2003). Another study from Russia reported an incidence of ADRs in 16.9% of the cases (Mishin *et al*, 2003). In contradiction to these findings, our study reported a lower rate of ADRs. It might be because our study was a retrospective one and hence certain minor ADRs might have not been documented. Another study from the United Kingdom reported an incidence of 5.1% (Ormerod and Horsfield, 1996) which is lesser than ours.

In our study, females had a higher incidence of ADRs. In general, females are at higher risk of developing ADRs (Puavilai and Timpatanapong, 1989). It might be because they pass through life stages like pregnancy, menarche etc, which modify the drug response (Wilson, 1984). Studies from the UK and Canada also reported females to have a significantly higher incidence of ADRs due to ATT drugs (Ormerod and Horsfield, 1996; Yee *et al*, 2003). This suggests the need for special precautions while prescribing ATT drugs to females.

The most common system affected by the ADRs was hepatobiliary. In a study from the neighbouring country, India on ADRs due to ATT drugs majority of the patients (53%) had gastrointestinal reactions, the commonest presenting complaint being nausea and vomiting (Dhingra *et al*., 2004). A similar observation was made from Russia also (Chukanov *et al*., 2004). The most common ADRs associated with the ATT drugs in our study were related to the liver. Several studies have documented the hepatotoxic effect of ATT drugs (Rossouw and Saunders, 1975). A study from Nepal reported an incidence of 8% hepatotoxicity to ATT drugs (Shakya and Rao, 2004). ATT induced hepatotoxicity can be severe and lead to mortality. The principal clinical risk factors for hepatotoxicity are old age, malnutrition, alcoholism, HIV infection, as well as chronic hepatitis B and C infections (Yew and Leung, 2006). There are several strategies to prevent the occurrence of these ADRs. Drug-induced hepatic dysfunction usually occurs within the initial few weeks of the intensive phase of anti tuberculosis chemotherapy (Yew and Leung, 2006). It is also recommended that liver function should be studied every two weeks during ATT to prevent serious hepatotoxicity (Wada, 1998). A few guidelines were also published mentioning the management of hepatotoxicity due to ATT drugs (BTS guidelines, 1998; Harries *et al*., 1998). It is also the responsibility of the health care professionals to counsel the patients regarding the early signs of hepatotoxicity.

Identifying the drugs causing ADRs is an important responsibility of the healthcare professionals and can prevent the occurrence of similar ADRs in future. In our study, INH, rifampicin and pyrazinamide caused almost an equal number of ADRs. A study from Russia reported streptomycin as the drug responsible for more ADRs (Mishin *et al*, 2003). There can be differences among the drugs causing higher number of ADRs and it depends mainly on the type of regimen used, dose of the drugs, genetic make up of the population etc.

Onset of the ADRs is an important factor helpful in early detection of the ADRs. In our study, more than half the ADRs occurred within the first 30 days of the initiation of ATT. Also in a study from India (Dhingra *et al*, 2004), 67% of the ADRs occurred in the first four weeks. It is essential for the healthcare professionals to counsel the patients regarding the early identification of ADRs in the first few weeks. Regular monitoring of the patients during these initial weeks might be essential for early detection of ADRs.

The most common laboratory abnormality observed was derrangement in the hepatic enzymes. Since hepato-toxicity is the most common ADR, there were more number of patients with liver enzymes derrangement. Nearly 17% of the patients developing the ADRs needed drug therapy for the management of ADRs. These ADRs were mainly dermatological.

Carrying out the causality assessment using standard methods is one of the best ways to establish the causal relationship between the drug and effect. The Naranjo algorithm (Naranjo *et al*, 1981) is used widely in carrying

out the causality assessment of ADRs. It is based on the score calculated on the basis of points given for each of ten questions that comprises the algorithm. On a scale of 13, if the score is greater than 9, then the adverse reaction is categorized as definitely caused by the particular drug. A score of (5-8) is categorized as probably caused by the drug while a score of (1-4) is categorized as possibly caused by the drug. We found majority of the ADRs had a probable relationship with the suspected drug. However, nearly 7.5% of the ADRs had a 'definite' relationship with the suspected drug.

In order to take appropriate initiatives towards the management of the ADR, it is necessary to study the severity of the ADRs. Hartwig scale (Hartwig *et al*, 1992) is widely used for the purpose. This scale categorizes the reported adverse drug reactions into different levels as mild, moderate or severe. In Mild (Level 1) the ADR requires no change in the treatment with the suspected drug and Mild (Level 2) the ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in lenght of stay. In Moderate (Level 3) the ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/ or an antidote or other treatment is required with no increase in length of stay. Moderate [Level 4 (a)] is any level 3 ADR that increases the length of stay by at least one day and in Moderate [Level 4 (b)] the ADR is the reason for admission. The Severe (Level 5) is any level 4 ADR that requires intensive medical care, Severe (Level 6) is the ADR causing parmanent harm to the patient and Severe (Level 7) being the ADR either directly or indirectly leading to the death of the patient. In our study, majority of the ADRS were of Mild [Level (1)] type. There was only one ADR which was responsible for hospital admission.

Limitations: Our study had a few limitations. The study was a retrospective one and hence may not have detected minor ADRs due to lack of documentation. We also could not obtain the files of 167 patients who were treated during the study period because their files were not stored in the Medical Records Department. This might have influenced our data.

CONCLUSION

The present study identified the pattern of ADRs experienced by the patients on ATT. Females had a higher incidence of ADRs. Hepatobiliary ADRs were the most common type and the most common laboratory abnormality was the derrangement of liver enzymes. Majority of the ADRs were 'minor' and had a 'probable' relationship with the suspected drugs. Since TB is a common problem in Nepal, special emphasis is needed to tackle the drug related complications associated with ATT drugs.

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