A study of adverse drug reactions caused by first line anti-tubercular drugs used in Directly Observed Treatment, Short course (DOTS) therapy in western Nepal, Pokhara

Anupa Khatri Chhetri[1], Archana Saha[2], Sharat Chandra Verma[3], Subish Palaian[4], Pranaya Mishra[5], Pathiyil Ravi Shankar[6]

Department of Pharmacology[1,2,4,5,6], Western Regional Tuberculosis Centre[3], Manipal College of Medical Sciences, Pokhara, Nepal.

Abstract

Objective: To study the Adverse Drug Reactions occurring during DOTS therapy and to assess their causality, severity and predisposing factors.

Method: Patients undergoing DOTS treatment during the 5 month study period (20th January to 20th June, 2005) at the Regional Tuberculosis Center (RTC) in Pokhara, Western Nepal were studied. Patients and/or patient party were interviewed to detect occurrence of any ADRs during their visit to the DOTS center. Causality and severity assessment were carried out as per the 'Naranjo scale' and 'modified Hartwig and Siegel scale' respectively. Statistical analysis (Chi square test) was done to determine the predisposing factors.

Results: Totally 137 patients were studied among whom 54.74% (n=75) reported occurrence of ADRs. Total 29.33% of ADRs were reported by the age group 21- 30 years. Nearly half (49.33%) of the ADRs were reported by men and 33.33% were reported by the ethnic group of 'Gurungs'. Half (49.33%) of the patients were illiterate and 70.67% of the ADRs were classified as ADRs 'possibly' due to the suspected drugs and 93.33% were classified as 'mild (level 1)'. Isoniazid accounted for 49.3% of the ADRs. The most commonly reported ADR was tingling and burning sensation in hands and feet experienced by 32 (11.03%) patients.

Conclusion: Occurrence of ADRs from antitubercular drugs was high in the population of Western Nepal. Further studies encompassing a wider population and covering different regions of Nepal are needed (JPMA 58:531; 2008).

Introduction

Tuberculosis (TB) is a bacterial infection caused by organisms belonging to the Mycobacterium tuberculosis complex.[1] The World Health Organization (WHO) declared TB as a global emergency in 1993.[2] In Nepal, about 60% of the economically active population has been infected with TB. Over 80,000 people in Nepal have TB, about 44,000 people develop TB every year and nearly half of them, 20,000 have infectious sputum positive TB and pass the disease on to others.[3] Despite the development of modern health services throughout much of Nepal, many people still do not have access to effective TB treatment. An estimated 6,000- 8,000 people die from TB every year in Nepal.[3]

Worldwide, several initiatives have been taken to combat TB, one of the most important being the "DOTS" (directly observed treatment, short course) strategy. DOTS is a methodology for making sure that every patient starting TB treatment gets the best chance of being cured. The patients take their medicines everyday under the direct observation of a healthcare worker or some other responsible person. The treatment course lasts from 6-8 months and includes therapy with the drugs; isoniazid, rifampicin, pyrazinamide, ethambutal and streptomycin. In Nepal, the DOTS strategy was adopted by the National Tuberculosis Program (NTP) in 1995.[3]

The World Health Organization (WHO) has defined ADR as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[4] Some common ADRs due to the antitubercular drugs are visual disturbances, peripheral neuropathy, jaundice, skin rashes, pancreatitis, hyperuricaemia, ototoxicity and hypersensitivity reactions.[5]

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.[6] It has been found that 50% of the ADRs are preventable in the first place.[7] Worldwide, many countries have started ADR monitoring programmes 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.[8] Manipal Teaching Hospital (MTH), a tertiary care teaching hospital in Pokhara, Western Nepal, has started spontaneous reporting programme at the hospital level since September 2004.[9]

In view of the high prevalence of TB and widespread use of antitubercular drugs, it has become the need of the hour to monitor for ADRs and increase awareness of ADRs among consumers in the Nepalese population. Data regarding ADRs due to anti tubercular therapy (ATT) are scant in Nepalese population. Hence, the present study was carried out with the objectives, to study the ADR pattern due to first line anti-tubercular drugs used in DOTS strategy in Nepalese population in Pokhara, Western Nepal, to study the predisposing factors and to carry out the causality and severity assessment of the reported ADRs.

Patients and Methods

The study was done in the Regional Tuberculosis Center (RTC), Pokhara, Western Nepal. The RTC is the regional center for the diagnosis and treatment as well as referral centre for TB patients in Western Nepal. It monitors and manages TB control activities of Western Region of Nepal comprising of 16 districts. The present study was conducted for a period of 5 months (20th January 2005 to 20th June, 2005).

The target population was Tuberculosis infected patients undergoing antitubercular treatment (ATT) with first line drugs in DOTS center at RTC. Any patient undergoing treatment at the time of study was included. Patients who were lost to follow up within one month, uncooperative or unwilling to be enrolled, or appeared unreliable were excluded.

The various study tools used were the Patient profile form which recorded all the information, such as name, age, sex, location, literacy, ethnic group, socioeconomic status, life style factors and dietary factors, pregnancy status (for female patients) and outcomes of delivery and birth in case of pregnant patients, any concurrent diseases and medications other than antitubercular agents that the patients might be taking. ADR Reporting Form recorded all the essential information regarding the adverse effects: the onset and severity of the ADR experienced, the impact of ADR on the treatment and work capacity of the patient, the drug(s) involved, the date of starting the suspected drugs and the date of reporting of the ADR. Naranjo Algorithm[10] is used to categorize ADRs as possibly, probably or definitely due to a certain drug. It is based on the score calculated on the basis of points given for each of ten questions that comprises the algorithm. Modified Hartwig and Siegel scale[11] categorizes the reported ADRs into different levels as mild, moderate or severe based on the treatment and requirement of hospitalization for the management of the ADRs. Both these scales were also employed.

Regular visits to the RTC DOTS center were made by the researchers during the study period. The patients satisfying the inclusion criteria were enrolled after obtaining verbal consent and were followed up for five months. Information on any past or current occurrence of adverse effects due to the ATT drugs being administered to them was collected from the patients directly by the researchers. However, in very few cases, the responses were obtained form the attendants in the absence of the patient. The data was statistically analyzed using SPSS version 9.0 and Chi-square test was used to determine the association between the ADRs and the different population parameters. The results obtained were then compared with those documented in the literature.

Results

A total of 137 patients were included in the study among whom more than half [n=75 (54.74%)] reported experiencing ADRs. Table 1 gives the distribution of ADRs reported in different age groups. The occurrence of ADRs was almost equal among male (49.33%) and female (50.67%) patients. The result was not statistically significant (P= 0.364.) We found that twenty five (34%) of the patients experiencing the ADRs were 'Gurungs' followed by 'Brahmins' 16 (21%), 'Dalits' 12 (16%), 'Chhetri' 7 (9%) and others 15 (20%). Statistical analysis also showed a positive association between the ethnic group 'Gurung" and occurrence of ADRs.

Table 1: Age distribution.

S. No	age group (years)	No of patients (%) Developed ADRs	Not developed ADRs
1	0-20	12 (16)	15 (24.18)
2	21-40	31 (41.33)	27 (43.54)
3	41-60	21 (28)	12 (19.34)
4	>60	11 (14.66)	8 (12.89)

X^2 = 2.538 P = 0.468

We categorized the literacy of the patients as illiterate (uneducated), literate (able to read and write). Occurrence of ADRs was almost equal in both literates and illiterates with 37 (49.33%) literate patients and 38 (50.66%) illiterates patients reporting ADRs. This result, however was not statistically significant (P= 0.455).

Table 2 gives the prevalence of ADRs among the population with varying life style factors like smokers, non-smokers, former smokers, alcoholics, former alcoholics, non-alcoholics, vegetarians and non-vegetarians and users or non users of chewing tobacco.

Of the reported ADRs, 53 (71%) were classified as possible and the remaining 22 (29%) as probably caused by the suspected drugs as per the Naranjo algorithm.[10] Isoniazid was considered to be responsible for nearly half of the reported ADRs (49.3%), pyrazinamide for 22.7%, rifampicin for 18.7% streptomycin for 5.3% and ethambutal for 4%.

Altogether a total of 290 ADRs were experienced and details are listed in Table 3. Majority of the ADRs were related to the Central nervous system 46 (61.33%), followed by Musculo-skeletal system 40 (53.33%), Gastro intestinal system 34 (45.33%), skin 25 (33.33%), Respiratory system 3 (4%), Endocrine system 3 (4%), Vestibular system 3 (4%), Ocular system 2 (2.66%) and Cardiovascular system 1 (1.33%). The reported ADRs were classified into different levels like mild, moderate or severe based on the Modified Hartwig and Siegel scale. Most (98.67%) of the reported incidences of ADRs were classified as mild level 1 and 1.33% as moderate level 3.

Table 2: Association of life style factors and occurrence of ADRs.

S.No	Parameters		No of patients (%) Developed ADRs	Not developed ADRs	X^2 value p value
1	Smoking status	Former smokers	32 (42.62)	23 (37.09)	X^2 =1.914
		Current smokers	3 (4.00)	7 (11.29)	P= 0.397
		Non smokers	40 (53.33)	32 (51.6)	
2	Alcohol consumption	Former alcoholics	27 (36.00)	18 (29.03)	X^2 =1.712
		Current alcoholics	1 (1.33)	1 (1.61)	P= 0.425
		Non alcoholics	47 (62.67)	43 (69.35)	
3	Tobacco chewing	Former users	7 (9.33)	8 (12.90)	X^2 =0.129
		Current users	8 (10.66)	4 (6.5)	P= 0.937
		Non users	60 (80.00)	50 (80.64)	
4	Dietary factor	Vegetarians	3 (4.00)	0 (0)	X^2 =2.495
		Non vegetarians	72 (96.00)	62(100)	P= 0.114

The association of incidence of ADRs and different population parameters was studied and the possible predisposing factors found were age (the age group (21-30) years was seen to have the maximum incidence of ADR (29.33%) and the age group (0-10) years had lowest reported incidence (1.33 %)), sex (there was almost equal

Table 3: Types of adverse drug reactions experienced by the patients (n=290).

S.No	ARD Reported	No. of Cases	Percentage
1	Tingling and burning sensation in hands and feet	32	11.03
2	Joint pain	30	10.34
3	Back pain / muscle pain / Body ache	30	10.34
4	Epigastric pain / Epigastric burning	30	10.34
5	Dermatological manifestations (Generalized itching / itchy rashes)	29	10.00
6	Anorexia / Nausea /Vomiting	28	9.66
7	Vertigo/ Dizziness	18	6.21
8	Headache	14	4.83
9	Weakness	10	3.45
10	Tinnitus	7	2.41
11	Ataxia	5	1.72
12	Fever	4	1.38
13	Shortness of breath on mild exertion	4	1.38
14	Constipation	3	1.03
15	Diarrhea	3	1.03
16	Agitation	3	1.03
17	Cough	3	1.03
18	Edema of feet	3	1.03
19	Pain at site of injection	3	1.03
20	Burning sensation in eyes	2	0.69
21	Dim vision	2	0.69
22	Nocturnal leg cramps	2	0.69
23	Water brash	2	0.69
24	Miscellaneous	23	7.93

prevalence of both male and female reporting ADRs. No association between gender and occurrence of ADR was found by statistical analysis, ethnic groups (Statistical analysis showed positive association between the occurrence of ADRs and the ethnic group 'Gurung'), literacy (there was almost equal prevalence of ADRs among the illiterate (49.33%) and literate (50.67%). No association of occurrence of ADR was found with literacy levels, life style and dietary factors (maximum ADRs were reported by non smokers, non alcoholics, non users of chewing tobacco and non-vegetarian patients. Statistical analysis showed no association between the various life style and dietary factors and the occurrence of ADRs.

Discussion

A total of 137 patients were enrolled in the study, among which 75 (54.74%) developed ADRs. This result is much higher than the result of the study by Mishin et al,[12] where ADRs were found to occur only in 16.9% of cases. As the mentioned study was carried out in Russian population, the difference in results could have resulted due to the genetic, demographic and nutritional status differences among the two populations. In another study carried out in Nepalese population by Koju et al,[13] ADRs were reported by 80% of the population.

In this study, majority of ADRs were reported by the age group 21-40 years. This result is in contrast to the study by Yee et al where age over 60 years was associated with increased incidence of ADRs due to anti TB drugs.[14] In another study by Shakya et al, patients of younger ages 18-20 years were seen to be more prone to anti-TB drug induced hepatotoxicity.[13,14] In a study by Gronhagen-Riska C et al,[15] elderly women were considered a risk group for hepatitis induced by isoniazid- rifampicin treatment in TB. The results of this study could have been due to the reason that the age group 21-40 years included majority of the patients undergoing treatment at the RTC DOTS center. Moreover, in this study, no laboratory investigations were done to detect asymptomatic hepatotoxicity; it could not be detected which age group was more predisposed to this particular adverse effect of the anti TB drugs. No association was found between age and incidence of ADRs during the statistical analysis.

Female patients experiencing ADRs were only slightly more in our study than the male patients. A study by Yee et al,[14] and Shakya et al[16,17] considered female gender as a risk factor for the occurrence of ADRs due to anti-TB drugs. Generally, females are considered to be more at risk of ADRs due to their smaller body size and body weight compared to males. However, our study failed to establish the association between gender and incidence of ADRs.

Among the different ethnic groups, most ADRs were reported by the ethnic group 'Gurung'. This could have been because the population of the study area predominantly consists of Gurungs and majority of the patients undergoing treatment at the RTC DOT centers were the same. Since statistical analysis also showed a positive association between ethnicity and occurrence of ADRs it can be concluded that the ethnic group 'Gurung' is at greater risk for ADRs from anti-TB drugs. This result could not be compared with any other similar studies as no other studies relating to the incidence of adverse effects of anti TB drugs in different ethnic groups of Nepalese population could be found.

In this study, occurrence of ADRs was more or less equal in the literate and illiterate populations. This could have been because any patient who could read and write was considered literate. This result also could not be compared with any other studies as again we were unable to find any study associating literacy with occurrence of ADRs due to anti-TB drugs.

From the different life style factors the most reported ADRs in this study were associated with non-smokers, non-alcoholics, non-users of chewing tobacco and non-vegetarians. The result of an 11- year study by Dossing et al.[18] has concluded that the risk factors of hepatoxicity included old age, female sex and extensive tuberculosis but not alcoholics. However, in the study by Gronhagen-Riska C et al,[15] alcoholics were considered a risk group for the occurrence of ADRs induced by isoniazid and rifampicin. In our study, current alcoholics and smokers were very few and no specific laboratory investigations were done to detect asymptomatic hepatic toxicities. These reasons could have caused the difference in results seen in our study and those reported in other studies. Statistical analysis also could not establish any significant association between the various life style factors and the incidence of ADRs.

The majority of the ADRs reported in this study were categorized as 'possible' as per the Naranjo algorithm signs and symptoms were enquired. No dechallenge or rechallenge was done to establish the causative agent, placebo effect was not studied, and no laboratory investigations were done to determine the concentration of drug in body fluids or tissue. Owing to the lack of all these parameters, none of the reported ADRs could be classified as 'definite' attributed to the suspected drugs.

In this study, (61.33%) of ADRs reported involved the central nervous system. The highest reported ADR was peripheral neuropathy, characterized by a tingling and burning sensation in the hands and feet. INH was considered to be the suspected drug responsible for peripheral neuropathy. This conclusion was made based on the literature evidence suggesting maximum incidence of peripheral neuropathy due to this drug.[19] Moreover, it is known that peripheral neuropathy is the most common side effect of INH, occurring in about 20% of patients receiving 6 milligrams per kilogram per day without supplemental Pyridoxine. The other anti TB drug known to cause peripheral neuropathy is Ethambutol, but very rare in comparison to INH.[19]

We failed to confirm the exact causative agent responsible for this ADR as we could not carryout the rechallenge. In a study conducted by Koju et al,[13] peripheral neuropathy was experienced by only 18.57% of the patients, which is much lower than the results of this study. In the existing literatures also, occurrence of peripheral neuropathy is considered rare with the recommended doses of isoniazid used in DOTS strategy.[2] In the study by Mishin et al,[12] streptomycin was identified as the most frequent agent for ADRs caused by a single leading agent in patients with pulmonary TB. This could have been because this study was carried out on a Russian population and genetic and demographic variations could have influenced the results. The result of this study could also have been different because majority of the patients undergoing treatment at the RTC DOTS center were of lower socioeconomic status and could have been malnourished. Also, pyridoxine was not included in the standard DOTS regimen and many patients reporting with the symptoms of peripheral neuropathy were either unwilling or unable to buy pyridoxine due to their poor economic condition. Hence, inclusion of pyridoxine in the standard DOTS regimen for developing countries like Nepal where a majority of the population are under the poverty line, seems to be a much needed necessity.

Among the reported ADRs in our study, 93.33% was classified as mild (level 1) ADRs and 6.66% as moderate (level 3) ADRs as per the modified Hartwig and Siegel scale. Level 1 ADRs requiring no change in treatment with the suspected drug occurred in 70 patients (93.33%). Among the 5 patients (6.66%) with level 3 ADRs, the dose of streptomycin had to be reduced and subsequently stopped in 1 patient and 4 patients were prescribed and took pyridoxine. Although more patients were prescribed pyridoxine and non-steroidal anti-inflammatory drugs (NSAIDs) for complaints of peripheral neuropathy and arthralgia, none seemed willing and/or able to buy and take the prescribed medications. In most of these patients, adverse effects were seen to abate spontaneously over a period of time. In a study by Gonzalez Montaner et al,[20] the frequency of adverse effects of anti TB drugs causing changes in therapeutic regimens was reported to be 6.5%, which is in agreement to the result of this study.

Limitations

Laboratory investigations to determine plasma or tissue drug concentrations, liver function tests, haematological tests, serum uric acid or acetylator status of the patients were not done. Data obtained from interview of patient's family in the absence of the patient might not have been totally accurate. Rechallenge, dechallenge could not be done and placebo effects could not be observed while carrying out the causality assessment.

Conclusion

Though the incidence of ADRs due to first line antitubercular drugs used in the DOTS strategy in Pokhara, Western Nepal, was high, majority of the reported ADRs were classified as mild and did not need modification of treatment or administration of specific antidotes. Majority of the patients were seen to have mistaken the symptoms of ADR to be due to the disease being treated. The study concluded that there is a need of a system for proper monitoring for ADRs due to antitubercular drugs. Counseling of patients for timely prevention, detection and management of ADRs was also highly suggestive.

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References

1. Bennet PN, Brown MJ. Clinical pharmacology. 9th ed. Edinburgh: Churchill Livingston, 2003, pp 237- 55.
2. Nehaul LK.Tuberculosis. In: Walker R, Edwards C, eds. Clinical Pharmacy and Therapeutics. 3rd ed. Edinburgh: Churchill Livingston, 2003, pp 583-95.
3. Neil Hamlet,Sushil Chandra Baral. Case Study of National Tuberculosis Programme Implementation in Nepal. [Online] 2002. Available from URL: http://siteresources.worldbank.org/NEPALEXTN/Resources/publications/tuberculosis_study.pdf. Accessed on June 23, 2006.
4. World Health Organization. Requirements for adverse reaction reporting. Geneva, Switzerland; 1975.
5. Leuenberger P, Zellweger JP. Drugs used in tuberculosis and leprosy. In: Dukes MNG, Aronson JK, eds. Meyler's side effects of drugs. 14th ed. Amsterdam: Elsevier, 2000, pp 1005- 29.
6. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse Drug Reactions. Br Med J 1998 ; 316:1295- 8.
7. Winterstein AG, Sauer BC, Hepler CD, Poole C. Preventable drug-related hospital admissions. Ann Pharmacother 2002; 36: 1238-48.
8. Drug Bulletin of Nepal. [Vol 15: No-2 Online] Dec 2004 - Mar 2005 [Cited 2006 Jun 23]. Available from: URL: http//www.dda.gov/publication/dbn-vol16.pdf. Accessed on June 23, 2006.
9. Palaian S, Mishra P, Shankar PR, Dubey AK, Bista D, Almeida R. Safety monitoring of drugs- Where do we stand? Kathmandu Univ Med J 2006; 4: 119-27.
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45.
11. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992; 49: 2229-32.
12. Mishin VIu, Vasil'eva IA, Makieva VG, Kuz'mina NV, Prikazchikova AV, Khoroshutina VV. Frequency, pattern, and diagnosis of adverse reactions in patients with pulmonary tuberculosis during chemotherapy with leading drugs. Probl Tuberk Bolezn Legk 2003; 7: 24-9.
13. Koju D, Rao BS, Shrestha B, Shakya R, Makaju R. Occurrence of side effects from anti- tuberculosis drugs in urban Nepalese population under DOTS treatment. Kathmandu University J. Sci, Engineering and Technol, 2005; 1.
14. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first- Line antitiberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2003; 167: 1472-7.
15. Gronhagen-Riska C, Hellstrom PE, Froseth B. Predisposing factors in hepatitis induced by isoniazid-rifampin treatment of tuberculosis. Am Rev Respir Dis 1978; 118: 461-6.
16. Shakya R, Rao BS, Shrestha B. Management of antitubercular drugs-induced hepatotoxicity and therapy reintroduction strategy in a TB clinic of Nepal. Kathmandu Univ Med J (KUMJ) 2005; 3: 45-9.
17. Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. Ann Pharmacother 2004; 38: 1074-9.
18. Dossing M, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11- year study. Tuber Lung Dis 1996; 77: 335-40.
19. Klasco RK (Ed): DRUGDEX® System. Thomson Micromedex, Greenwood Village, Colorado, Vol. 133 (Edition expires [9/2007]).
20. Gonzalez Montaner LJ, Dambrosi A, Manassero M, Dambrosi VM. Adverse effects of antituberculosis drugs causing changes in treatment. Tubercle 1982; 63: 291-4.