KATHMANDU UNIVERSITY JOURNAL OF SCIENCE, ENGINEERING AND TECHNOLOGY
VOL.I, No.1, SEPTEMBER, 2005.

OCCURRENCE OF SIDE EFFECTS FROM ANTI-TUBERCULOSIS DRUGS IN URBAN NEPALESE POPULATION UNDER DOTS TREATMENT

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ABSTRACT
Tuberculosis is one of the foremost public health problems causing an enormous burden of suffering and deaths. Chemotherapy is the basic approach to clinical tuberculosis control. [1]Essential anti-tuberculosis drugs are Isoniazide (INH), Rifampicin (RMP), Pyrazinamide (PZA), Ethambutol (E) and Streptomycin (S). Department of Pharmacy, KU, KUTH, and Dhulikhel conducted this study in collaboration with German-Nepal Tuberculosis Project (GENETUP) and Korea-Thimi Friendship Hospital during March 2005 to July 2005. Total 70 newly diagnosed pulmonary or extra-pulmonary tuberculosis patients were included in the present study. Patients were kept under observation during whole treatment period. Clinical, hematological and biochemical monitoring form the basis of diagnosing side effects due to anti-tuberculosis therapy. Among the 70 cases studied, 70% were male and 30% were female. There was significant increase in the bilirubin total, bilirubin direct, AST, ALT, alkaline phosphatase, eosinophils, lymphocytes, monocytes after anti-tuberculosis treatment whereas there was significant decrease in WBC count, neutrophils, platelets count, and ESR after anti-tuberculosis treatment. Serum level of creatinine was normal before and after anti-tuberculosis treatment. In our study, slight increase in uric acid level was detected after anti-tuberculosis treatment when compared to pretreatment, though it was in the normal range. Of the 70 patients treated for tuberculosis, 80% of the total number of patients reported at least one type of side effects. 24 patients (34.29%) had experienced major side effects. 8 elderly patients (44.44%) and 16 younger patients (30.76%) had experienced major side effects. Female gender (38.10%), alcoholics (38.89%) and sputum-smear positive (32.14%) were associated with increased occurrence of major side effects. The overall side effects indicate that side effects are not to be neglected. It was experienced that timely detection and temporary withdrawal of the offending agent can completely cure anti-tuberculosis drugs-induced side effects. For this, careful patient monitoring clinically, hematologically and biochemically especially during first few weeks of chemotherapy and patient counseling regarding side effects of the anti-TB medications are necessary.

Key Words: Tuberculosis, DOTS, Anti-tuberculosis drugs, Side effects

INTRODUCTION
Tuberculosis causes a great deal of ill health in the populations of most low-income countries; it is the single most common cause of death in individuals aged fifteen to forty-nine years.

The world adopts DOTS strategy for TB control thought the national TB control programs in different countries and is making good progress. DOTS stands for Directly Observed

Treatment-Short course. In Nepal, DOTS strategy has been implemented since 1996 and has already reduced the number of deaths. Expansion of this cost effective and highly successful treatment strategy of DOTS, which already has proven its efficacy in Nepal, will have a profound impact on mortality and morbidity (NTC, 2001/2002).

The currently recommended anti-tuberculosis regimens are usually well tolerated. However some patients may experience problems, usually due to the bulk of the drugs, a single day's dose consisting of 6-7 tablets. Drug related side effects might be minor or major. In general, a patient who has minor side effects should be encouraged to continue the treatment with symptomatic measures such as antacids, antihistamines, antiemetics, or analgesic. If major side effects occur, the regimen, or the offending drug, if identified, must be stopped. Further management depends on the nature of side effects and may have to be done in a hospital.

It has been very important to draw attentions of all health workers towards side effects of anti-tuberculosis drugs since side effects can be harmful to the patients. Pharmacists have an ethical obligation to notify the appropriate bodies whenever side effects are suspected. The decision to report such cases should not dependent on whether the potential side effects are already well known. Instead, pharmacists are encouraged to report any suspected side effects. Side effects of anti-tuberculosis drugs is already well known, further report on the occurrence will be helpful in minimizing if not avoiding this undesirable effect. Hence, it has been attempted to find the occurrence of anti-tuberculosis drug- induced side effects in urban Nepalese population.

MATERIAL AND METHOD

Study site: The study was conducted on the patients of German Nepal Tuberculosis Project (GENETUP) and Korea-Thimi friendship hospital.

Patients: From March 2005 to July 2005, a prospective cohort evaluation of anti-tuberculosis drugs-induced side effects in urban Nepalese people was undertaken. A total 60 newly diagnosed tuberculosis patients, attending at GENETUP, Kalimati, Kathmandu and 10 patients attending at Korea-Thimi Friendship Hospital, Thimi, Bhaktapur were included in the present study.

The study comprises 55 patients with new pulmonary tuberculosis and 15 patients with extra-pulmonary tuberculosis. Among 15, 7 had tuberculosis pleural effusion and 8 with tuberculosis lymphadenopathy.

Sample Collection: Written informed consent was taken from each patient enrolled in this study. After taking the consent of the patient, Patient Information Form was filled.

Before initiating therapy, pre-treatment of biochemical tests such as bilirubin total, bilirubin direct, AST, ALT, alkaline phosphatase, creatinine and uric acid were monitored by measuring their serum level. Similarly, pretreatment of hematological tests such as WBC count, neutrophils, eosinophils, lymphocytes, monocytes, platelets count, and ESR were measured.

Blood samples were collected through vein puncture. About 5 ml of venous blood were collected. Sterile syringe of having 5 ml capacity was used for the collection of blood.

For biochemical tests, about 3 ml blood samples were taken. It was centrifuged and serum was separated into clean, dry, sterile vials and stored at -20^0 c for analysis. Biochemical tests were done using the routine laboratory process with the help of semi auto-analyzer.

For hematological tests, about 2 ml blood samples were taken and mixed in a tube containing EDTA. Both biochemical's as well as hematological tests were done in the pathology lab of Dhulikhel hospital using routine laboratory process.

After initiating the drug therapy, biochemicals as well as hematological tests were performed biweekly for as long as one month. Patients were kept under observation during their whole treatment period. Patients were instructed to report any signs and symptoms they will come across during the treatment period.

Statistical Analysis: From the observation pretreatment vs. post treatment after one month of treatment were analyzed separately by paired t-test. Statistical analysis was performed using SPSS version 11.0

RESULTS AND DISCUSSION

A total 70 cases during March 2005 to July 2005 were included in the study. Among the studied 70 cases of tuberculosis, males (70%) were found higher in number than females (30%).

The study showed that 80% of patients reported they had experienced at least one type of side effects. However, most of the reactions were minor and required no modification of treatment. The result of our study is in agreement with the clinical study done in Japan, which showed the side effects appeared in 90% of the patients.[2]

The results of the present study showed serum bilirubin, AST, ALT and ALP was significantly higher in tuberculosis patients after treatment when compared to pretreatment. Elevated levels of bilirubin, AST, ALT, alkaline phosphatase after treatment in tuberculosis patient have been noted in many studies; [3-5] these observations are further confirmed in this study.

To test nephrotoxicity, creatinine test was included in this study. Serum level of creatinine was normal before and after anti-tuberculosis treatment. It may be due to not using of Streptomycin in the patients enrolled in this study. One of the side effects of Streptomycin is nephrotoxicity. Streptomycin is not used in category I and category III patients which are included in the study.

Uric acid test was done to test hyperuricemia. In our study, slight increase in uric acid level was detected after treatment when compared to pretreatment, though it was in the normal range. This increase may be due to Pyrazinamide whose one of the side effects is hyperuricemia. The result of the present study was in agreement with the study of Zierski M et.al. (1980), which showed the elevation of serum uric acid on Pyrazinamide therapy.[6]

In a study done by Nagayama N et al (2004) in Japan, it was found that the leucopoenia appeared in 1.2% men and 5.9% female. But in contrast, WBC count was normal before and after anti-tuberculosis treatment though there was decrease in WBC count after treatment when compared to pretreatment.

Bacterial infection such as tuberculosis may cause neutropaenia. Hence neutrophils are estimated. Although there was decrease in neutrophils after treatment when compared to pretreatment, it was in the normal range. The result of the present study was in agreement with the study of Umeki S. (1989) in Japan.[2]

Bacterial infection such as tuberculosis may causes eosinophilia. Hence eosinophils are estimated. Although there was increase in eosinophils after treatment when compared to pretreatment, it was in the normal range. The result of the present study was in agreement with the study of Umeki S. (1989) in Japan.[2]

Tuberculosis may cause lymphocytosis and monocytosis. Hence both are estimated. Although there was increase in both cases after treatment when compared to pretreatment, both were in the normal range.

To test thrombocytopenia, platelet count was included in the study. Although there was decrease in platelet count after treatment as compared to pretreatment, it was in the normal range. This decrease in platelet count may be due to Rifampicin whose one of the side effects is thrombocytopenia. The result of the present study was in agreement with the study of Nagayama N et.al (2004) in Japan.[7]

This study confirmed the fact that decreases in ESR level is related with the duration of anti-TB therapy. Before starting DOTS, ESR was found to be high and after one-month treatment with DOTS, diminished level of ESR value was found in tuberculosis. This showed significant efficacy of the anti-tuberculosis drugs.

Symptom Based Approach to Side Effects of Anti-Tuberculosis Drugs[8]:

Minor side effects: In this study, 34 patients (48.57%) experienced nausea. Similarly, 8 patients (11.43%) experienced vomiting, 3 patients (4.29%) diarrhea and 16 patients (22.86%) experienced anorexia. The drugs, which are responsible for these side effects, may be Pyrazinamide and Rifampicin.

Abdominal pain was experienced by 11 patients (15.71%). The drugs, which are responsible for this side effect, may be Pyrazinamide, Rifampicin and Isoniazid.

Itching without rash was experienced by 27 patients (38.75%). The drugs, which are responsible for this side effect, may be Pyrazinamide, Rifampicin and Isoniazid.

Twenty-nine patients (41.43%) experienced joint pain (arthralgia). The drug, which is responsible for this side effect, may be Pyrazinamide.

Thirteen patients (18.57%) experienced burning sensation in feet. Isoniazid may be the responsible drug for this side effect.

Major side effects: Of the 70 patients treated for tuberculosis, 24 patients (34.29%) had major side effects. Among them, 9 patients (12.86%) experienced jaundice. The drugs that are responsible for this side effect may be Pyrazinamide, Rifampicin and Isoniazid.

Three patients (4.29%) experienced skin rash. The drugs, which are responsible for this side effect, may be Pyrazinamide, Rifampicin and Isoniazid.

In addition, 18 patients (25.71%) experienced flu syndrome. The drug, which is responsible for this side effect, may be Rifampicin.

ACKNOWLEDGEMENT
Authors thank Dhulikhel Hospital, German-Nepal Tuberculosis Project (GENETUP) and Korea-Thimi Friendship Hospital for supporting this initiative. The generous support from Kathmandu University is gratefully acknowledged.

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Table 1: Profile of tuberculosis patients enrolling in this present study

Variables	Frequency	Percent
Sex		
Male	49	70%
Female	21	30%
Age		
15 to 35	52	74.3%
36 and above	18	25.7%
Disease extent		
Sputum positive	56	80%
Sputum Negative	14	20%
Alcohol intake		
Alcoholic	36	51.4%
Non alcoholic	34	48.6%

Table 2: Pretreatment and post-treatment biochemical as well as hematological tests in 70 tuberculosis patients

Variables	Pretreatment (mean ± SD)	Post Treatment (mean± SD)	P Value
Bilirubin total, mg/dl	0.86± 0.15	1.17±0.53	0.000
Bilirubin direct, mg/dl	0.18±0.06	0.44±0.40	0.000
AST, IU/L	29.09±7.35	45.66±14.62	0.000
ALT, IU/L	31.63±6.45	55.63±18.49	0.000
Alkaline phosphatase (Normal range 98-306U/L)	241.20±59.28	315.39±60.86	0.000
Creatinine, mg/dl	0.93±0.17	1.08±0.19	0.000
Uric acid, mg/dl	4.47±0.77	4.63±0.74	0.266
WBC, /cu mm	7324±1847	6345±1181	0.000
Differential leucocytes count:			
Neutrophils, %	61±6	56±6	0.000
Eosinophils, %	2±1	3±2	0.026
Lymphocytes, %	35±8	40±6	0.000
Monocytes, %	2±1	3±2	0.005
Platelet, /cu mm	239,171±65,344	207,328±35,180	0.002
ESR, mm/hr	38±12	32±10	0.001

Definition of abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; WBC= White blood cells; ESR= Erythrocyte sedimentation rate.

Table 3: Symptom- based Approach to Side Effects of Anti-tuberculosis Drugs

Minor Side Effects:

	Side Effects	Frequency	Percent
1	Nausea	34	48.57%
2	Vomiting	8	11.43%
3	Anorexia	16	22.86%
4	Abdominal Pain	11	15.71%
5	Itching, No Rash	27	38.57%
6	Joint Pains	29	41.43%
7	Burning Sensation in feet	13	18.57%

Major Side Effects:

	Side effects	Frequency	Percent
1	Jaundice	9	12.86%
2	Skin rash	3	4.29%
3	Flu Syndrome	18	25.71%

Other Side Effects:

	Side effects	Frequency	Percent
1	Bitter taste	2	2.86%
2	Angina	2	2.86%
3	Diarrhea	3	4.29%
4	Constipation	3	4.29%
5	Sweating	1	1.43%
6	Insomnia	1	1.43%
7	Body pain	1	1.43%

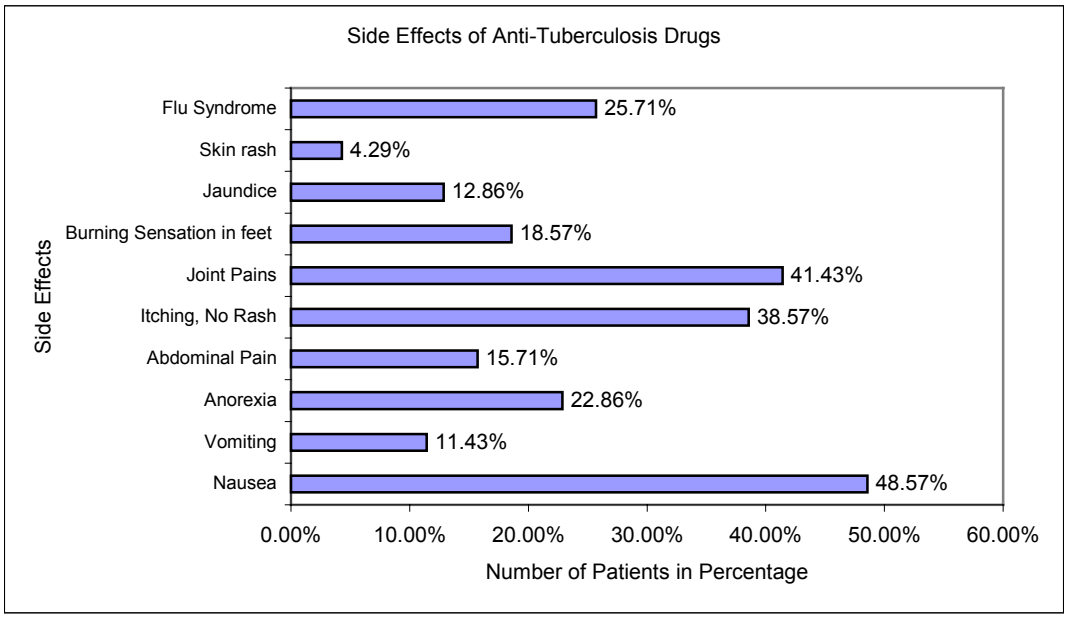

Fig 1: Symptom-based Approach to Side Effects of Anti-tuberculosis Drugs

Table 4: Age, gender, disease extent, alcohol intake in patients experiencing major side effects (jaundice, skin rash, flu syndrome)

Major side effects	Frequency	Percent
Total	24	34.29%
Sex		
Male	17	34.69%
Female	8	38.10%
Age		
15 to 35	16	30.76%
36 and above	8	44.44%
Disease extent		
Sputum positive	18	32.14%
Sputum negative	4	28.58%
Alcohol intake		
Alcoholic	14	38.89%
No alcoholic	10	29.41%

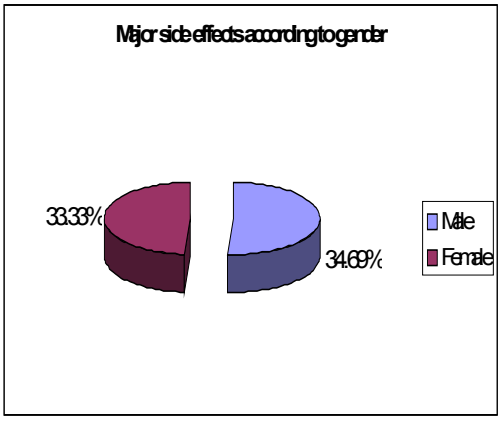

Fig 2: Comparison of major side effects in male and female gender

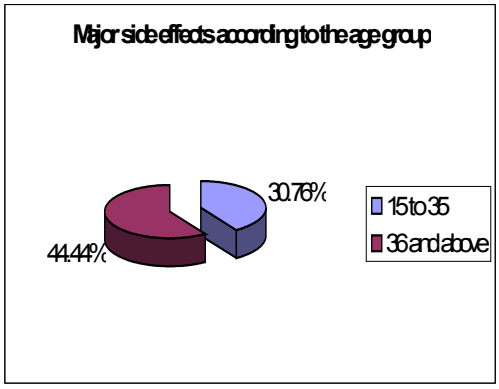

Fig 3: Comparison of major side effects in different age groups