Management of antitubercular drugs-induced hepatotoxicity and therapy reintroduction strategy in a TB clinic of Nepal

Shakya R[1], Rao BS[2], Shrestha B[3]
[1]Lecturer, [2]HoD, Department of Pharmacy, Kathmandu University, [3]Director, German Nepal Tuberculosis Project

Background: PZA, INH and R have potential for hepatotoxic side effects. Although anti-tuberculosis drug-induced hepatotoxicity is well known, there is no agreement on the clinical approach for cases in whom hepatotoxicity has developed. **Objective:** To study the management of anti-TB-drugs induced hepatotoxicity and the standard anti-TB drugs therapy reintroduction procedure. **Design:** In prospective cohort analysis, 4 patients with active TB infection had developed anti-TB drugs induced hepatotoxicity. Retreatment of therapy was done on the basis of severity of hepatitis. If damage is mild, all the drugs were reintroduced at once in a tapering dose and if patient's condition is worse, INH and E is introduced in lower dose, later increasing the dose and the number of drugs. **Results:** All the patients tolerated anti-TB drugs well after reintroduction. There was no incidence of recurrence. All the patients completed their 8 months treatment regimen and all are cured. **Conclusion:** Timely detection and temporary withdrawal of the offending agent can completely cure anti-TB drugs-induced hepatotoxicity. The recurrence of hepatotoxicity is rare if reintroduction in done in a well planned manner.

Tuberculosis (TB) has become enormous problem and the most effective control method is drug treatment, to cure the infection with antituberculosis drugs (anti-TB).[1] Directly Observed Treatment short course (DOTs), based on WHO framework, was introduced in Nepal in 1995 for effective control of TB. The overall goal of the National TB Programme is to reduce the mortality, morbidity and transmission of TB to such a level that it becomes no longer public health problem.[2,3] Now a day, with the help of short course chemotherapy, the treatment of tuberculosis is highly efficacious with low relapse rates.

Despite of being effective chemotherapeutic agent, hepatotoxicity from first line drugs such as isoniazid (INH), rifampicin (RMP), and pyrazinamide (PZA) is common and may limit their use and often can lead to interruption of the therapy. Two of these four agents (INH and PZA) are major hepatotoxins. The remaining two agents (RMP and ethambutol, E) are rarely or not hepatotoxic.[4] However, RMP, which is a powerful enzyme (cytochrome P450) inducer, may increase the metabolism of INH, so, increases the formation of hepatotoxic metabolite of INH.[5] The association of several antitubercular drugs has a benefit that it prevents drug resistance but at the same time adds the risk of hepatotoxicity of individual drugs.

Hepatotoxicity is a common complication of antituberculosis therapy that ranges from asymptomatic elevation of serum transaminases to hepatic failure requiring liver transplantation.[6]

Mortality rates depend critically on early detection. If drug therapy is discontinued promptly when greater than 3-fold elevation of transaminases occurs, mortality will be negligible. In contrast, if INH is continued after this point or after symptoms develop, mortality due to hepatic failure may exceed 50% unless liver transplantation is performed. The factor of greatest clinical importance for the development of severe hepatotoxicity is probably continuation of treatment once hepatic dysfunction has initiated.[7]

With the increasing incidence of tuberculosis worldwide, a greater number of patients are exposed to the risks of a potentially serious hepatotoxic effect of antituberculosis drugs. Although anti-tuberculosis drug-induced hepatotoxicity is well known, there is no agreement on the clinical approach for cases in whom hepatotoxicity has developed.[8,9,10] This study was done with the aim of studying management of antituberculosis drugs-induced liver dysfunction in Nepal.

Correspondence
Rajani Shakya
Lecturer, Department of Pharmacy
Kathmandu University
Email: rajani@ku.edu.np

Methodology

Patients

The study was conducted in German Nepal TB Project (GENETUP) from December 2001 to October 2002. The study comprises 37 patients with new pulmonary tuberculosis and 13 patients with extra pulmonary TB. Among 13, 6 had tuberculous pleural effusion and 7 with tuberculous lymphadenopathy. All the patients were between 15 to 57 years of age. There were 22 females and 28 male patients enrolled in the study. Patients were included in the study by the method of randomization.

The patients fulfilled following criteria: they were negative for HBsAg, anti-HCVAb, and HIV. At the beginning of treatment, liver function tests (LFT) showed completely normal findings on serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase (ALP), albumin and total protein. Patients receiving other potential hepatotoxic drugs in addition to anti-TB drugs and the relapsed cases of TB were excluded. 50 patients who fulfilled above stated criteria were selected from the total of 128 patients registered in the clinic during the study period. Patients gave written informed consent after approval by the ethics committee of the clinic.

Drug regimen

Treatment was planned as recommended by our National Tuberculosis control Programme (NTP). Total treatment period was 8 months, comprising intensive phase of 2 months followed by continuation phase of 6 months (Table 2). Doses were fixed according to the total body weight of the patient.
Doses were as follows: INH: 300mg/day for all body weights, RMP: 300 mg (for 25-39 kg), 450 mg (40-54 kg), 600 mg ($\geq$ 55 kg), PZA: 1000 mg (25- 39 kg), 1500mg (40-54 kg), 2000 mg ($\geq$ 55 kg), E: 800 mg (25-39 kg), 800 mg (40-54 kg), 1200 mg ($\geq$ 55 kg). Patients were taking medicines daily under direct supervision of medical staffs of the clinic.

Diagnosing criteria for drug-induced hepatotoxicity[11]
Normalization of liver enzymes level and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti-TB drugs, and presence of at least one of the following criteria: a rise to five or greater than five times the normal level of ALT and/or AST; a rise in the level of serum total bilirubin over 1.5 mg/dl; any increase in AST and/or ALT above pretreatment levels together with anorexia, nausea, vomiting and jaundice.

Normal maximum value in the laboratory is 35 IU/L for ALT and for AST; it is 40 IU/L. For ALP normal upper limit is 115 IU/L.

Study Design

A prospective cohort evaluation of anti-TB drugs-induced hepatotoxicity in Nepalese people was undertaken. Before initiating drug therapy, after taking written consent from the patient, pretreatment LFTs were conducted. After initiating the drug therapy, LFTs were performed after a week, then biweekly for at least two months. Patients were kept under observation during the whole treatment period. LFTs were repeated later whenever symptoms suggestive of hepatotoxicity like nausea, malaise, vomiting or jaundice occurred. Patients were instructed to report any signs and symptoms they will come across during the treatment period.

Anti-TB drug therapy was stopped promptly as the patients developed drug-induced hepatotoxicity (DIH). Treatment was withheld until the patient's biochemical reports normalized. Within few days of cessation of drugs, liver enzymes returned to the normal level. After the serum transferase level have normalized and plateaued reinstitution of anti-TB therapy was done.

Reintroduction of the drugs was done depending upon severity of hepatotoxicity. If the patient had severe hepatotoxicity, clinically as well as biochemically, INH and E were started at low doses initially (100 mg and 400 mg of INH and E respectively). Patient was kept on this regimen for about a week with close monitoring during that period. If the patient remained asymptomatic and liver biochemistry remained normal during that period, then other drugs, RMP and PZA were introduced in smaller doses (150 mg and 250 mg of RMP and PZA per day). Later within few days, if there is no further reaction, doses of all drugs were increased up to the standard chemotherapeutic regimen.

If the hepatotoxicity cases were not so severe, then, all of the drugs were reintroduced at once but in tapering doses. At the beginning, patients were given low dose of drugs; INH 100 mg/day, RMP 150 mg/day, PZA 500 mg/day. Amounts were increased on the alternate days with closely monitoring the patient. If there is further reaction full dose of standard chemotherapy will be continued.

Data analysis

From the observation, rates of hepatotoxicity were determined from the population beginning antituberculosis therapy. Elevations in serum AST and ALT levels (Pretreatment vs. serum level after one month of treatment) were analyzed separately by paired t-test. Statistical analysis was performed using SPSS version 10.0.

Results

There were 28(56%) male and 22(44%) female, with ages ranging 15 to 57 years (mean 30.5±14.5 years). A total of 37 (74%) had active pulmonary tuberculosis and 7(14%) had tuberculous lymphadenopathy and remaining 6(12%) had tuberculous pleural effusion.

It was observed that administration of anti-TB drugs caused elevation of liver enzymes in all the cases (t = - 5.467, P = 0.00, P<0.05 for ALT and t = - 4.55, P = 0.00, P<0.05 for AST).

During the study period, 4 out of 50 patients with active TB developed hepatotoxicity detected by clinical examination and confirmed by liver function tests. So, it is identified that 8% of the Nepalese urban population is susceptible to hepatic adverse effect of anti-TB drugs.

Symptoms shown by all patients were almost the same. They had shown gastrointestinal manifestations like nausea, vomiting, abdominal discomfort, anorexia and jaundice. Due to this anti-TB therapy were stopped temporarily until their clinical and biochemical picture normalized. Rest of the patients continued treatment without complications, and liver enzymes normalized within few days of continued treatment.

The time interval from initiation of treatment to the onset of hepatotoxicity was a mean of 31.75 ± 20.238 (12 – 60) days; the time from withdrawal of drugs to resolution of hepatotoxicity was a mean of 17.5 ± 4.041 (14 – 21) days. (Table 1)

Patients belonging to younger age group were found to be at higher risk for anti-TB drugs-induced Body mass index of our patients were low (BMI < $20kg/m^2$) and their serum albumin levels were less than 3.5 mg/dl. Malnourishment may be one of the risk factors of anti-TB drugs induced hepatotoxicity. 3 patients developing hepatotoxicity had severe TB, proven microbiologically as well as radiologically. Probably, the extent of disease has a role in predisposing the patient towards hepatotoxicity

It was observed that all the four patients who had developed hepatotoxicity tolerated the drug after reintroduction. There was no recurrence of hepatotoxicity in any of the patients. They completed their anti-TB treatment successfully without any further complications. They were treated for the full eight months period and all were cured.

Table1. Duration of the onset of hepatotoxicity and peak level of enzymes at the onset of hepatotoxicity.

Case no.	Age (yrs)	Gender	Weight (kg)	Date of treatment started	Date of onset of hepatotoxicity	Peak AST/ ALT/ ALP at the onset of hepatotoxicity (IU/Lt)
1.	47	Female	30	01/12/13	02/01/02	85.4/53.0/284.0
2.	18	Female	32	01/12/31	01/01/12	69.0/43.0/264.0
3.	20	Female	43	02/01/24	02/03/22	84.0/63.0/382.0
4.	20	Male	50	02/02/06	02/03/02	224.5/210.5/109.5

Discussion

Hepatotoxicity is one of the main side effects of the drugs used in TB treatment. Patients were confirmed of anti-TB drugs-induced hepatotoxicity both by biochemical test, by measuring serum level of ALT, AST and ALP and also clinical monitoring of their signs and symptoms. In the present study, 4 out of 50 patients, which accounts for 8%, developed hepatotoxicity, which is higher than previous studies from USA and UK.[10]

Once the hepatotoxicity has occurred, all the drugs are withdrawn and retreatment is started only when all biochemical markers have returned to normal levels. It is well-accepted fact that the risk of adverse effect must be balanced with the benefits of effective TB treatment. Prolong interruption of treatment may lead to undesired drug resistance and may prolong the therapy.[12]

In the present study, reintroduction of anti-TB therapy was done according to the severity of hepatotoxicity. In the case of mild hepatotoxicity, all drugs were reintroduced at once, initially in lower doses, which were increased on subsequent days with daily monitoring of patient's clinical and biochemical conditions. Three of the patients had mild hepatotoxicity with mild jaundice and the symptoms shown were alleviated as soon as the therapy was halted. It seemed possible to reintroduce all the drugs at once. So, all the drugs were reintroduced at once but in tapering dose.

If the patient had developed severe hepatotoxicity, then after recovery from hepatitis, low dose of INH and E was reintroduced, and patient was kept on strict observation. If the patient's LFT remained normal and patient remained asymptomatic for a week, then other drugs were added, first day on low dose, increasing on subsequent days.

All the patients were kept under observation for whole the treatment period. None of the patients had reoccurrence of hepatotoxicity later. They completed their anti-TB treatment successfully without any further complication. So, this study revealed that it is possible to reintroduce potentially hepatotoxic agents easily after recovery.[12,13] Mechanism for this adaptation is not known. It was felt that gradually introducing the drugs by giving them in increasing number and dosage is the reason for the successful retreatment procedure.[10,14] This effect is believed to be the avoidance of hypersensitivity reaction due to the administration of all the drugs at once in high dose.[15,16] So, careful dose selection of drugs to be used in retreatment and the pattern of dose increment is of paramount importance. Isoniazide and rifampicin are essential in tuberculosis treatment, and in regimens that do not contain any one these drugs; the treatment success rate is compromised. Withdrawal of a drug such as INH or RMP during the initial phase may cause incomplete initial phase treatment. In countries such as ours, where primary drug resistance is high, this can lead to acquired drug resistance. And also treatment period will increased to 12 – 18 months instead of 8 months.[17] Again, there are some controversies on whether or not to use PZA in retreatment after hepatotoxicity. Some studies have reported fatal hepatic necrosis caused by PZA.[18,19] But no such incidence was experienced in the present study. All the patients tolerated PZA well without recurrence of hepatotoxicity. Studies conducted in animal models of tuberculosis have demonstrated that the ability of PZA in combination with INH to sterilize tuberculous lesion more rapidly than INH alone. It was also suggested that PZA has dose dependent toxicity. In doses of 1 - 2 gm daily, the incidence of hepatotoxicity is much lower.

It was experienced that timely detection and temporary withdrawal of the offending agent can completely cure anti-TB drugs-induced hepatotoxicity. Patients who ultimately die or require liver transplants because of anti-TB drugs-related fatal hepatitis frequently have a history of continuing to take these medicines after symptoms of hepatotoxicity, including jaundice have appeared.[20] Although there is no reported controlled study, there are different opinions on how to perform retreatment after hepatotoxicity has resolved.[14] The aim of the management of hepatotoxicity in these patients must be to maintain cure of the disease, without liver damage. Clinical and laboratory monitoring throughout the retreatment is of great importance in order to detect hepatotoxicity. Our NTP has not adopted the protocol of routine liver function test during anti-TB chemotherapy. And also our patients, who are mainly form poor socioeconomic status, cannot afford the high cost of LFT. To minimize possible risks, health care providers should carefully monitor patients for adverse effects. Patients should be informed about symptoms of hepatitis and instructed to discontinue use of medicines if symptoms occur and to contact their health care provider.

In conclusion, reintroduction of anti-TB drugs was possible after complete resolution of DIH. There was no recurrence of hepatotoxicity in patients with gradual reintroduction of a retreatment regimen. Regular clinical evaluation of patients is recommended, and educating patients regarding signs and symptoms of hepatitis should be continually reinforced.

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