Original Article

Investigation of Hepatotoxicity of Antituberculosis Medications in some Hospitals, Khartoum State

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ABSTRACT

Background: Tuberculosis (TB) is an ancient disease still kills more than two million people every year, despite the fact that a cure has been available for over 50 years. Some antituberculosis agents cause hepatotoxicity as a major adverse drug reaction.

Objectives: This study was designed to investigate rifampicin, isoniazid and pyrazinamide induced-hepatotoxicity among TB patients in Sudan.

Methods: Sudanese in-patients (n=57) their ages ranged between 15 to 76 years, with active pulmonary tuberculosis and normal pretreatment liver function, received rifampicin (10 mg/Kg/day), isoniazid (5 mg/Kg/day) and pyrazinamide (20 mg/Kg/day) daily for two months, were involved in this study. Liver function test was performed for each patient separately at week 8, 9 and 10, to assess direct and indirect bilirubin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, albumin and total protein levels.

Results: Liver function tests revealed that 10 (17.5%) patients had high serum total bilirubin level, whereas 46 (80.7%) of them showed significant alteration in direct (conjugated) bilirubin level. Five (8.7%) and 23 (40.3%) patients demonstrated increased serum level of alanine aminotransferase and alkaline phosphatase respectively. Moreover, 15 (26.3%) of the treated patients experienced higher serum levels of aspartate aminotransferase. Hepatotoxicity and symptoms of liver failure occurred in 9 (15.7%) patients, which necessitate treatment discontinuation. Thirty eight (66.6 %) of the treated patients developed alteration in serum albumin level, whereas slight alteration in total protein level was found in 12 (21%) of the TB patients.

Conclusions: Biochemical investigations and clinical monitoring of patients treated with antituberculosis drugs are essential to decrease hepatotoxicity of these agents.

Key words: Tuberculosis; Rifampicin; Isoniazid; Pyrazinamide; Hepatotoxicity; Liver Function Tests.

In 24 march 2005 (world day of tuberculosis), the International Union Against Tuberculosis and Lung Disease (IUATLD) reported that: tuberculosis is an ancient diseasestill kills more than two million people every year despite the fact that a cure has been available over 50 years. With nearly 25000 people developed tuberculosis on daily basis, approximately one-third of the world's population (2 billion) people are infected with tuberculosis. Of these numbers 95% of the new cases occur in developing countriesThe impact of tuberculosis produces greater determinant in the developing countries because it generally affects the most economically active segment of the population, those between the age of 15 and 54[1].WHO reports stated that tuberculosis is a global emergency since it is one of the most widely prevalent infectious diseases affecting millions of human population in general and in the developing countries in particular [2].

There are different treatment regimens used for tuberculosis therapy[3]. The WHO recommended a regimen (6-9 months) consisting of rifampicin, isoniazid, pyrazinamide and/or ethambutol for the initial

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two months followed by a further four months of rifampicin and isoniazid[4]. Although most patients tolerate antituberculosis drugs, some agents may cause adverse effects and many drug interactions including gastrointestinal disturbances and hypersensitivity reactions[3]. The incidence and severity of unwanted reaction are related to dosage and duration of administration. The major adverse effect of rifampicin, isoniazid and pyrazinamide is hepatotoxicity[4]. The patient receiving these drugs may often undergo liver function test for determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin levels. The enzyme AST is mainly a liver enzyme and in general the increase in serum levels of both AST and ALT indicates liver cell damage associated with the two drugs, isoniazid and rifampicin. This is confirmed by the high level of the enzyme ALP that occurs mainly in the disorders of the liver,biliary tract and bone[5, 6].
In Sudan the treatment of tuberculosis follows the Sudan TB module guidelines for both adult and children. It consists of two phases, the initial phase in which a daily use of at least three drugs (rifampicin, isoniazid, pyrazinamide or ethambutol) for two months and the continuation phase using two drugs (rifampicin and isoniazid) in full sensitive cases for a further four months. Ethambutol can be omitted from the regimen if the resistance to isoniazid is low[7]. Streptomycin is scarcely used if resistance to isoniazid has been confirmed before tuberculosis therapy is started[8].
Indian studies for patients with pulmonary tuberculosis treated with rifampicin and isoniazid showed that these drugs induced hepatotoxicity. This adverse drug reaction is common and it is potentially fatal[9, 10].
The present study was an attempt to investigate the hepatotoxicity of antituberculosis therapy in TB patients in some hospitals of Khartoum State.

Materials Methods

Study population

This study was conducted at Elshaab, Abuaanga and Suba Hospitals, Khartoum State, Sudan, during the period of 15th August up to 20th October 2006. Three hundred patients were selected to participate in this study and were diagnosed with positive sputum smear tuberculosis test (Zn. test) and had chest X-ray findings compatible with active pulmonary tuberculosis. All the patients had pretreatment evaluation clinically especially for evidence of liver disease, history of alcoholism or concomitant drug therapy.
The TB patients fulfilled the following criteria: Patients suffering from previous hepatic disease or infected with hepatitis virus as well as those with high alcohol consumption or using hepatotoxic drugs and/or drugs that may enhance hepatotoxicity, pregnant ladies and children below 15 years old were excluded (n=243). This study was approved by the ethics committees in the three hospitals.

Treatments regimen and blood sampling

The patients were treated daily with isoniazid 5 mg/kg/day (GMC, Ltd, Sudan, maximum dose 300 mg/day), rifampicin 10 mg/Kg/day (GMC, Ltd, Sudan, maximum dose 600 mg/day) and pyrazinamide 20 mg/Kg/day (Microlabs Pharmaceutical, India, maximum dose 2000 mg/day) for two months. Liver function tests were performed at week 8, 9 and 10 for each patient separately.
The TB patients were monitored clinically as well as biochemically. The treatment of the participants was under control in all cases. All treatment was self-administered; patients were continuously evaluated for signs and symptoms of adverse events by especialists of chest diseases and assessed for adherence to treatment.
After 2 months of continuous treatment, 5 ml of blood were drawn from the orbital plexus by nontoxic, pyrogen free sterile disposable syringe at week 8, 9 and 10 for each patient separately.
The blood samples were collected in lithium heparin containers and after 5 minutes of centrifugation (2000 rpm) the obtained supernatant serum samples were frozen at -20C^{o} until they were analyzed for total liver function test using Roche Hitachi 912

Chemistry Analyzer (F. Hoffmann Roche Ltd, Switzerland). This apparatus was found in research and laboratory unit, Khartoum teaching hospital. It is mainly used for analysis of various body fluids and it is fully automated, computerized and performed potentiometric and photometric assays. It consists of photometric measuring system, analytical processing unit, screen and printer. The analyzer characteristics included 200 photometric tests per hour and refrigerated storage for 40 reagent containers. For serum determination of bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin and total protein levels, 0.5 ml of serum sample for each patient was placed in the apparatus separately registered in the screen and results were printed within 10 minutes for each parameter.

Statistical analysis

The data were subjected to completely randomized design. Analysis of results were carried out using simple t-test and mean separations were conducted to test significant difference of groups with the aid of SPSS computer program version 14.

Results

The participants in this study were 57 patients, their ages ranged between 15 to 76 years and the mean age being 39.7 ± 18.3 years and weighing 61.6 ± 11.3 kg. The male-to-female ratio of those patients was 2.4:1 (Table 1). Before treatment the liver function tests for all patients, were normal.

The present study revealed that 10 (17.5%) patients received antituberculosis chemotherapy showed increases in serum total bilirubin level, ranged between 1.2-1.6 mg/dl, slightly greater than the normal level of total bilirubin (0.1-1 mg/dl). Also there was significant alteration in serum direct (conjugated) bilirubin level in 46 (80.7%) patients, ranged between 0.1-0.5 mg/dl, while normal limit is 0.0-0.25 mg/dl[6, 11] (Table 1). Accordingly, small proportion of patients developed jaundice. These findings agreed to the results published by Sanches, *et al*., (2004) who described the hepatoxicity of both isoniazid and rifampicin that required a change of regimen or discontinuation of treatment[12].

Table 1: Number of patients with altered liver enzymes

		Liver enzymes						
		Bilirubin	D. bilirubin	ALT	ALP	AST	Alb	protein
Age(Years)	No of patients							
15-30	19	2	15	2	4	6	11	4
31-45	28	6	25	3	8	13	19	5
46- 60	6	2	4	0	1	1	4	1
61 -75	2	0	1	0	1	2	2	1
> 75	2	0	1	0	1	1	2	1
Total number of patients with altered liver function		10	46	5	15	23	38	12
Male	40	6	35	3	11	19	25	8
Female	17	4	11	2	4	4	13	4

Serum alanine aminotransferase (ALT) level was altered in 5 (8.7%) patients (Table 1), showed increases in the enzyme level, ranged between 52-92 U/L, exceeding the normal range of ALT (0.0-49 U/L). ALT is commonly used as a way of screening for liver problems; however, elevated level of ALTdoes not automatically mean that medical problems exist. Fluctuation of ALT level is normal overthe course of the day, and ALT level can also increase in response to strenuous physical exercise[13].

Table 1 indicated remarkable alteration in serum alkaline phosphatase (ALP) level in 23

(40.3%) of the treated patients. Most of them (n=19) demonstrated an obvious increases in the enzyme level and their concentrations ranged between 41-333 U/L, higher than the normal level of serum alkaline phosphatase (26-111 U/L). There was considerable alteration in serum aspartate aminotransferase (AST) level in 15 (26.3%) patients (Table 1), their serum levels ranged between 51-389 U/L, above the normal level (0-46 U/L). Hepatotoxicity and symptoms of liver failure occurred in 9 (15.7%) patients, which necessitate treatment discontinuation. It was reported that, in an intension to treatment analysis if 5% of the total patients developed grade three hepatotoxicity (>5 times of the normal range this showed the symptoms of hepatic failure) which required treatment discontinuation[12, 14].

As showed in Table 1, elevation in the serum total albumin developed in 38 (66.6%) of the treated patients. Of those 24 (63.1%) experienced increases in albumin level, their serum levels ranged between 4.4-4.8 g/dl while the normal range is 3.8-44 g/dl.

The alteration in the serum total protein (albumin, globulin and fibrinogen) level occurred in 12 (21%) of the treated patients was shown in Table 1. Six (10.5%) of them showed increases in serum total protein level (8.9-10.3 g/dl) greater than the normal range (6.4-8.8 g/dl)[12].

Discussion

Tuberculosis is a major health problem throughout the world, especially in the developing countries. The chronic use of antituberculosis medication is usually accompanied with hepatotoxic adverse reactions. The present study was carried out to evaluate the hepatotoxic effects of some drugs used in tuberculosis therapy particularly rifampicin, isoniazid and pyrazinamide.

The obtained results demonstrated that,hepatotoxicity as an adverse drug reaction was evident, common and potentially fatal. There were considerable changes in serum levels of bilirubin, ALT, ALP and AST, which are relatively common during antituberculosis chemotherapy, and may signify true organ toxicity. It appeared that for patients who are going to develop hepatotoxicity eventually, any elevation in AST levels three times greater than the upper limit of normal may easily become five times the upper limit of normal in due course. In the present study hepatotoxicity and symptoms of liver failure occurred in 9 (15.7%) patients, which necessitate treatment discontinuation. According to the American Thoracic Society recommendations antituberculosis drugs should be stopped when the serum transaminase level reaches three times the upper limit of normal for patients developing symptoms of hepatitis. The symptoms of gastrointestinal discomfort like anorexia, nausea, vomiting, epigastric distension, right upper abdominal discomfort, as well as other symptoms such as malaise and weakness are important[15] and the more relevant signs such as jaundice and hepatomegaly.

Combination of isoniazid with rifampicin and pyrazinamide increases the risk of antituberculosis medications induced hepatotoxicity[16-20] when compared with isoniazid monotherapy used for tuberculosis prophylaxis. Rifampicin is a drug of elative low toxicity when compared to isoniazid, although it is a potent liver metabolizing enzymes inducer that may enhance isoniazid hepatotoxicity[21]. Pyrazinamide also is most hepatotoxic antituberculosis medication like isoniazid. It was reported that, the mechanism of hepatotoxicity has been considered to be related to the dose and duration of administration[20].

Conclusion

Biochemical investigations and clinical monitoring of patients treated with antituberculosis drugs are essential to identify and/or to avoid hepatotoxicity of these agents. Treatment regimens with fewer potentially hepatotoxic agents might be beneficial for therapy of patients with tuberculosis. Patients counseling and education helps to minimize the risk of hepatotoxicity. Close clinical monitoring is essential and routine liver tests screening should be carried out before commencement of antituberculous drugs.

Patients with underlying hepatic abnormality pose a significant problem, since most drug-induced hepatotoxicity occurs within the initial two months of therapy, therefore closer monitoring at weekly/biweekly intervals for example, is recommended.

The early identification and modification of antituberculosis treatment are crucially needed for patients with increased risk of antituberculosis induced-hepatotoxicity, and hence reducing the morbidity and mortality.

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