

EVALUATION OF THE EFFECT OF ANTITUBERCULOUS DRUGS ON THE LIVER AND RENAL FUNCTIONS' TESTS IN A SUDANESE COHORT

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ABSTRACT

Tuberculosis (TB) is still a major problem in many countries. Despite the development of its powerful regimen, the treatment of tuberculosis continues to be a problematic. The Objective of this study to identify the effects of anti tuberculous drugs on renal and liver functions' tests in a Sudanese Cohort, and to evaluate the adopted monitoring procedures in the public hospitals in Sudan. Method: The study was a cohort prospective one; it was conducted among Sudanese patients, during the period from December 2009 to July 2010. The sample size was 100 patients randomly selected with tuberculosis and with normal liver and kidney functions. Renal and liver functions' tests were measured by spectrophotometric methods using the biosystem and flame photometer. The results: The study revealed that, renal function tests were changed after administration of the anti-tuberculous drugs in a significant value; mean plasma concentration of urea, creatinine, uric acid and potassium were increased while mean plasma concentration of sodium was decreased significantly. Liver function tests were also significantly altered; mean plasma concentration of bilirubin increased and the mean plasma concentration of the liver enzymes were increased significantly, while mean plasma concentration of total plasma protein and plasma albumin were significantly decreased. Conclusion: A set of recommendations was proposed to close catering for tuberculosis patients under treatment who accompanied by a history of renal and/or liver impairments.

Key words: Antituberculous, function test, liver, renal, Sudan.

INTRODUCTION

Tuberculosis (TB) is one of the most common infectious diseases globally. The World Health Organization (WHO) reports showed that there were an estimated 9.3 million incident cases and 13.7 million prevalent cases of TB in 2007¹. The WHO declared TB a global health emergency in 1993, and the Stop TB Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between 2006 and 2015². In 2004, around 14.6 million people had active TB disease with 9 million new cases. The annual incidence rate varies from 356 per 100,000 in Africa to 41 per 100,000 in the Americas³. The rise in human immune virus (HIV) infections and the neglect of TB control programs have enabled a resurgence of tuberculosis⁴. The emergence of drug-resistant strains has also contributed to this new epidemic TB, from 2000 to 2004, 20% of TB cases being resistant to standard treatments and 2% resistant to second-line drugs⁵. The most effective antituberculous (anti-TB) therapy is a combination of isoniazid (INH), rifampin and pyrazinamide (PZA) for 8 weeks, followed by isoniazid and rifampin for a further 4-7 months (standard therapy)⁶. Despite the development of this powerful regimen, the treatment of tuberculosis continues to be a problem in patients who do not tolerate these drugs⁷⁻⁹. If serious side-effects do occur and treatment with one of the three drugs must be finally terminated; the patient no longer receives the best treatment available and might be at a higher risk of treatment failure and relapse¹⁰. A major adverse reaction to one of the first-line antituberculosis drugs, which results in discontinuation of that drug, has several implications. There may be considerable morbidity, even mortality, particularly with drug-induced hepatitis^{11,12}. These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations^{12,13}. The occurrence, risk factors, morbidity, and mortality of adverse events from isoniazid (INH), particularly hepatotoxicity, have been well defined^{14,14,15}. Adverse reactions to rifampin (RIF) and ethambutol (EMB) have been well documented¹⁶⁻¹⁸. The incidence of major side effects associated with pyrazinamide (PZA), is somewhat controversial. Authoritative treatment guidelines have stated that "there does not appear to be a significant increase in hepatotoxicity when PZA is added to INH and RIF, based on results from large scale randomized trials". However, studies of patients treated for active disease, or receiving 2 months of RIF and PZA for latent infection, have reported serious adverse events attributable to PZA¹⁹. Alternative agents may have greater problems with toxicity, and are often less effective, so that treatment must be

prolonged, with attendant challenges to ensure compliance. As a result the risk of treatment failure and relapse are higher. The objective of this study was to identify the effects of anti-tuberculosis drugs on renal and liver functions' tests in Sudanese patients using antituberculosis drugs for more than three months. Other objectives were to evaluate the adopted monitoring procedures in the public hospitals in Sudan.

MATERIAL AND METHODS

Study design

The study was a cohort prospective one. It was carried out among a cohort of Sudanese patients in Abu Anja and Tropical Diseases public Hospitals in Omdurman-Sudan during the period from December 2009 to July 2010. The sample size was randomly selected 100 Sudanese patients, under treatment of tuberculosis with intact kidney and liver functions. Permission was obtained from concern authorities before the study was conducted. The objectives of the study were explained to all individuals participating in this study. Verbal and written consent was taken from the participants before commencing the study. Information about the study and its benefits was provided to all participants.

Methods: Therapy monitoring process was carried out for the selected patients. Blood sample 5 ml was collected from each patient. Serum was separated after clot retraction by centrifugation (at 3000 rpm), and the serum transferred to a stopper vial. Renal and liver functions' tests were measured by spectrophotometric methods using the biosystem and flame photometer by using commercial kits (Biosystem Company and Spinreact Company). The results were analyzed with the Statistical Package for Social Sciences (SPSS Version 17). Descriptive and comparative analysis was conducted. The 0.05 level of significant was used as a cutoff for statistical significant.

RESULTS

Regarding gender, male showed a dominance [n=84, 84.0%]. The mean average of respondents' age was 37 years (range 27 to 47 years). Renal and liver function tests monitoring was not routinely adopted throughout the period of tuberculosis therapy in [n=92, 92.0%] of the participants. The monitoring procedure revealed that, renal function tests were changed after administration of the anti-tuberculous agent in a significant value as shown in Table 1. Mean

plasma concentration of urea, creatinine and uric acid were increased significantly post drug administration as opposed to baseline as follows: [25.5 ±7.5 mg/dL vs. 87.7 ±21.8 mg/dL], [0.696 ±0.1 mg/dL vs. 3.642 ±1.6 mg/dL] and [3.55 ±0.829 mg/dl vs. 7.594 ±1.004 mg/dL]; respectively.

Mean plasma concentration of sodium was decreased by administration of the drugs from 136.46±3.418mmol/l to 127.38±4.009mmol/l. Mean plasma concentration of potassium before drug administration was found 3.908±0.412mmol/l and after drug administration was found 4.556±0.593mmol/l.

Table 1: Renal function tests before and after using the treatment of tuberculosis

Test parameter	Before using the drugs	After using the drugs	P-Value
Urea	25.5±7.552mg/dl	87.7±21.825mg/dl	0.001
Creatinine	0.696±0.164mg/dl.	3.642±1.646mg/dl	0.002
Uric acid	3.55±0.829mg/dl	7.594±1.004mg/dl	0.001
Sodium	136.46±3.418mmol/l	127.38±4.009mmol/l	0.003
Potassium	3.908±0.412mmol/l	4.556±0.593mmol/l	0.001

Table 2: Liver function tests before and after using the treatment of tuberculosis

Test parameter	Before using the drugs	After using the drugs	P-Value
Bilirubin	0.774±0.168mg/dl	4.126±1.512mg/dl	0.008
T.Plasma protein	6.99±0.607g/dl	5.358±0.352g/dl	0.003
Plasma albumin	4.028±0.430g/dl	2.772±0.307g/dl	0.002
AST	23.68±9.582 u/l	82.14±14.064 u/l	0.001
ALP	24.12±8.679 u/l	83.04±14.001 u/l	0.001
A.phosphatase	57.14±19.899 u/l	240.76±64.083 u/l	0.001

The plasma proteins and liver enzymes were significantly changed from the normal value by administration of antituberculosis agents. Table 2 shows that mean plasma concentration of bilirubin increased from 0.774±0.168mg/dl before drug administration to 4.126±1.512mg/dl after it. Mean plasma concentration of total plasma protein and plasma albumin were significantly decreased. Mean plasma protein was 6.99±0.607g/dl but after drug administration it became 5.358±0.352g/dl, while mean plasma albumin before drug administration was 4.028±0.430g/dl then decreased to 2.772±0.307g/dl. Mean plasma concentration of the liver enzymes were increased significantly above the normal value. Before drug administration mean plasma concentration of aspartateaminotransferase, alanineamino-transferase and alkalinephosphatase were post drug administration as opposed to baseline as follows: [23.68±9.582 u/l vs. 82.14±14.064 u/l], [24.12±8.679 u/l vs. 83.04±14.001 u/l] and [57.14±19.899 u/l vs. 240.76±64.083 u/l] respectively. The normal value of Aspartate aminotransferase, Alanine aminotransferase, and Alkaline Phosphatase are 5 - 30 U/l, 6 - 37 u/l and 30 - 90 u/l respectively

DISCUSSIONS

Renal and liver function tests monitoring was not routinely adopted throughout the period of tuberculosis therapy in 92.0% of the participants. Not monitoring antituberculous therapy may result in side effects, varying from minor to life-threatening side effects. The side effects of anti-tuberculous drugs prescribed for a patient with TB should be monitored. Different studies concluded that patients hospitalized for pulmonary tuberculosis need closer monitoring for side-effects^{20,21}. In our study, 100 patients treated with anti-tuberculous drugs were tested for the effect of these drugs on the kidney and liver functions. The study showed significant alterations of the kidney and liver functions' tests as a result of using antituberculous drugs. Liver tests were significantly affected by the use of anti-tuberculous drugs namely, hepatic functions' alteration was manifested by the increased plasma concentration of bilirubin and liver enzymes and decreased in plasma concentration of plasma proteins and albumin. These results were in agreement with different studies, that showed hepatotoxicity which resulted finally in termination of therapy²⁰⁻²². The current study also showed an alteration of renal function tests accompanied with administration of antituberculous drugs in terms of significantly increased plasma concentration of urea, creatinine, uric acid and potassium. According to Begum and co-workers, adverse effect parameters such as hepatic dysfunction and renal impairment were estimated before, two and eight weeks after initiation of anti-tuberculous drugs²³. The study findings were enhanced by Richard Zaleskis²⁴, who stated that nephrotoxicity is one of the serious major adverse effects caused by anti-tuberculous drugs.

The present data may provide a clear evidence of the increased risk of liver and renal impairment in the cohort of patients with tuberculosis, that severe enough to be treated in a hospital and denoted to be closely monitored.

CONCLUSION

The conclusion drawn from this study entails that serious adverse reactions to anti-tuberculous drugs were common and resulted in changes in liver and renal functions, increased hospitalization costs as well as prolongation of therapy. Such complications can easily be minimized if patients at risk were closely monitored in appropriate manner with frequent laboratory testing.

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