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Centre-based Evaluation of Some Biochemical Effects of the Initial Phase of Anti-tuberculosis Therapy in Bayelsa State

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Authors' contributions

This work was carried out in collaboration among all authors. Author BB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author OJK managed the literature searches. Authors RO and FCP managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aim of the Study: This study aimed at evaluating the adverse drug effects on some biochemical parameters of anti-tuberculosis drugs among patients with primary tuberculosis infection.
Study Design: Non-probability (purposive) sampling technique was employed in this study.
Place and Duration of Study: This study was carried out at the Chest Clinic unit of the Tuberculosis and Leprosy referral Hospital, Yenagoa, Bayelsa State, Nigeria. This study was conducted from July, 2017 to April, 2018.
Methodology: Tuberculosis patients were selected using standard methods for clinical diagnosis and confirmed by laboratory analysis for *Mycobacterium tuberculosis* using acid fast bacilli as preliminary and Gene-Xpert® as confirmatory test. A total of 44 tuberculosis patients met the study

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inclusion and exclusion criteria and completed the study at the Tuberculosis and Leprosy Referral Hospital Yenegoa, Bayelsa State. Eligible patients were administered with appropriate daily dose of (rifampicin-150 mg, isoniazid-75 mg, pyrazinamide-400mg and ethambutol-275 mg) single drug combination for two months based on bodyweight. Blood was collected and evaluated for liver enzymes, Alkaline phosphatase (ALP), Alanine transaminase (ALT), Aspartate aminotransferase (AST); Total proteins, Bilirubin and Cholesterol at baseline, week 4 and week 8. Data were descriptively analyzed using statistical package for social sciences (SPSS 21).

Results: Treatment in the intensive therapy phase resulted in significant increase of alanine aminotransferase and alkaline phosphatase levels (*P*=0.5). There was also significant decrease in total cholesterol and albumin (*P*=0.5). There were no significant changes in aspartate aminotransferase, total protein and total bilirubin.

Conclusion: The study results showed changes in some biochemical parameters but were not severe enough to warrant discontinuation of therapy.

Keywords: Adverse drug reaction; anti-tuberculosis drugs; biochemical parameters; GeneXpert.

1. INTRODUCTION

Despite the fact that most people in the developing countries are vaccinated at birth, tuberculosis is still a serious public health problem with more than 90% of new tuberculosis cases and deaths occurring in developing countries [1]. First line tuberculosis drugs recommended by World Health Organization are combinations of Isoniazid, Rifampin, Pyrazinamide, Ethambutol and Streptomycin [2,3]. The use of multi-drug regimen has been associated with increased incidence of adverse drug reactions and biochemical changes (4). The first line anti-tuberculosis drugs that are commonly used are highly effective but also can cause hepatotoxicity [4]. There is usually a transitory and asymptomatic increase in hepatic enzyme levels in 10-20% of the patients who use isoniazid in isolation, but there is an up to three-fold increase over the normal serum levels of the enzyme alanine aminotransferase which is more specific for liver damage than aspartate, aminotransferase but levels normalize as the treatment continues [5]. Transitory and asymptomatic increases in the serum levels of bilirubin and hepatic enzymes occur in 5% of patients treated with rifampicin. The level subsequently normalizes, without the need to discontinue the treatment. However, cholestatic hepatitis occurs in 2.7% of the patients receiving rifampicin in combination with isoniazid and in up to 1.1% of those receiving rifampin in combination with anti-tuberculosis drugs other than isoniazid [6,7]. Pyrazinamide is the most hepatotoxic of the antituberculosis drugs even though liver impairment is rare, if the drug is administered at a maximum dose of 35 mg/ kg/ day [6,8]. It is also known that serious side effects as a result of the therapy are worse during the intensive phase of treatment [9,10]. These assertions including therapeutic outcomes, systemic effects and adverse effects are reported in mostly whites and blacks in Diaspora [11]. There are no documented evidence of therapeutic outcomes, medication adverse effect of indigenous blacks living in Bayelsa State to the best of our knowledge. The scanty documentation where they exist mainly obtained from retrospective study mostly based on data from patient folders and other forms of review [12]. This study is to investigate prospectively the biochemical risks among active adults of the age of 15 years and above, of tuberculosis patients in Bayelsa State treated with anti tuberculosis therapy in the Tuberculosis and Leprosy Control Programme Hospital, Yenagoa, Bayelsa State.

2. MATERIALS AND METHODS

2.1 Study Location

The study was carried out following ethical approval at the Tuberculosis and Leprosy Control Programme Hospital, Yenagoa in Bayelsa State, Nigeria.

2.2 Inclusion Criteria / Exclusion Criteria

Included in the study were newly diagnosed *Mycobacterium tuberculosis* infected patients of either sex and of age 15years to 65years recruited after history, physical examination and investigations confirming the diagnosis of tuberculosis and who accepted to commence tuberculosis treatment according to the Nigerian national treatment guidelines for two months (intensive phase) of tuberculosis treatment.

Excluded patients were those with concomitant cardiovascular risks (hypertension, diabetes e.t.c), HIV/AIDS patients with or without currently being on Anti Retroviral Treatment (ART), renal and hepatic disorders and patients with resistance to rifampicin using Gene Xpert.

2.3 Study Population

Eligible patients (64) according to the inclusion criteria above were diagnosed using standard methods for clinical diagnosis and confirmed laboratory analysis for tuberculosis with smear positive results and Gene-Xpert® confirmatory routine tests. However, only 44 of these eligible patients completed the entire research process by compliance with the study criteria for 8 weeks.

2.4 Bacteriological Diagnosis of Tuberculosis

The bacteriological diagnosis of tuberculosis rested mainly on the identification of the tubercle bacilli by sputum smear microscopy for identification of acid fast bacilli using Ziehl-Neelsen staining method and Gene Xpert®confirmatory method that analysed the presence of mycobacterium DNA [13].

2.5 Sources of Drugs and Chemicals

The drugs used in this study include the oral first line drugs (intensive phase) for tuberculosis treatment namely R: rifampicin H: isoniazid E: ethambuthol Z: pyrazinamide fixed combination drugs formulation and sourced from the Nigerian Government partnership through the German Leprosy and Tuberculosis Relief Association (GLRA) [13]. The Gene Xpert, buffer solution, carbon fuchsin, methylene blue, 3% acid alcohol (Ziehl-Neelsen stain), Lysol, and Randox® reagents was obtained from donors and part of the supply used at the Tuberculosis and Leprosy control centre, Yenagoa Bayelsa State while the ELISA, Chemistry analyzer and reagents were procured through Tobis Clinic and Consultants Hospital laboratory services, Yenagoa, Nigeria.

2.6 Study Protocol

2.6.1 Drug administration

Eligible patients were administered with appropriate daily dose of the two month intensive phase drug regimen using the direct observation therapy, short course (DOTs).Biochemical parameters were monitored by laboratory investigations at baseline, week 4 and week 8.

Prior to commencement of drug administration venous blood samples were collected from each patients using 10 ml BD vacutainer tube (Becton and Dickinson, New Jersey), the gold caped tube with additive such as clot activator and gel for separation of whole blood for biochemical evaluation, at baseline and repeated at week four (4) and week eight (8).

2.6.1.1 Liver enzymes determination

Alkaline phosphatase was measured using the p-nitrophenol method (colorimetric method) described [14]. Biolabo® reference value is 90-390 U/L.

Aspartate aminotransferase (AST). This was assayed using the described method [15]. Biolabo® reference value is 13-31 IU/L.

Alanineaminotransferase (ALT). This was assayed using the method explained [15]. Biolabo® reference value is 10-40 IU/L.

2.6.1.2 Serum proteins determination

Total protein (TP). The assay was done according to described method [16]. Randox® reference value is 28-80 g/L.

Bilirubin (BIL). The assays was done based on described method [17] for assay of Direct (Conjugated Bilirubin) Randox® reference value is 5.20-606 µmol/L and Total Bilirubin (Randox® reference value is 5.20-606 µmol/L).

Albumin (ALB). This assay was done using the BCG dye binding method according to [18]. Randox® reference value is 28-50 g/L.

2.6.1.3 Serum lipids

The cholesterol oxidase method (enzymatic endpoint method) as described [19] was used.

Total cholesterol. The cholesterol oxidase method (enzymatic endpoint method) as described [19]. Randox® reference value is <5.17 mmol/L.

High density lipoprotein (HDL). Enzymatic endpoint method as described [19] was used for the assay of High density lipoprotein (HDL) (Randox® reference value is 1.04-1.55 mmol/L), Triglycerides (Randox® reference value is 0.4-1.8 mmol/L), Low density lipoprotein (LDL) calculated.

2.7 Statistics Analysis

Collected data were analyzed using Statistical Package for Social Sciences version 21.0 (SPSS 21. Results were expressed mean ± Standard error of mean (S.E.M). Statistical significance was place at *P*=.05.

3. RESULTS AND DISCUSSION

Isoniazid, pyrizinamide and rifampicin have been implicated for their hepatotoxic potentials reflecting by the progressive increased mean value result for the various liver enzymes at various stage of the study. Drug induced hepatic dysfunctions usually occurs within the initial weeks of the intensive phase of the anti tuberculosis chemotherapy [20].

The therapeutic effect on liver enzymes are marked, with ALP and AST showing more marked changes during the two months intensive phase therapy as shown in Table 1. This is consistent with the progressive rise in the liver enzyme especially of the ALP, ALT, and AST from baseline to the 8th week of the study. However, despite the apparent variation of these enzymes, ALP and ALT mean values were still within normal range while AST mean values though increasingly out of normal range were not statistically significant. Retrospective studies [21] showed significant changes in Alanine aminotransaminase in patients attending the tuberculosis and Leprosy control referral hospital in Yenagoa, Bayelsa State, which is consistent and corroborated by the mean values in our study.

The changes in Serum proteins were not totally considered significant, with total protein showing a mild increase from baseline to week 8, while ALB showed steady decrease from baseline as shown in Table 2. Bilirubin and total protein did not reflect significant changes with the anti-tuberculosis chemotherapy. The significant decrease in albumin is possibly the cause of some adverse effects as it is responsible for protein and drug binding and thus metabolism. The need for its replacement or supplementary diet is being advocated.

Table 1. Participants' liver enzymes levels at baseline, week 4 and week 8

Liver enzymes	Baseline	Week 4	Week 8
ALP (µ/L)	133.4 ± 4.5	163.7 ± 9.3*	188.1±11.9*
AST (µ/L)	14.8 ± 0.9	20.6 ± 1.4	24.8 ± 1.2
ALT (µ/L)	12.3 ± 0.9	14.8 ± 1.1*	14.8 ± 1.2*

*ALP = Alkaline phosphatase; AST = Aspartatetransferase; AST = Alanine transaminase. Data are expressed as Mean ± SEM of the changes in alkaline phosphatase, Aspartate transferase and Alanine transaminase levels. Data were considered statistically significant at P=.05. *- Significant*

Table 2. Participants' serum protein levels at baseline, week 4 and week 8

Serum proteins	Baseline	Week 4	Week 8
TP(g/L)	61.8 ±0.9	62.0 ±1.5	63.5±1.6
ALB(g/L)	38.3 ± 0.8	33.8±0.9*	30.8± 1.4*
TBIL (g/L)	11.1 ±0.8	11.1 ±0.6	11.9 ±0.7

*TP = Total proteins; ALB = Albumin; TBIL = Total bilurubine. Data are expressed as Mean ± SEM of the changes in Total proteins, Albumin, and Total bilurubine levels. Data were considered statistically significant at P=.05. *- Significant*

Table 3. Participants' serum lipids levels at baseline, week 4 and week 8

Serum Lipids	Baseline	Week 4	Week 8
CHOL (mmol/L)	2.8 ±0.1	2.6±0.1	2.5 ±0.1*
TRIG (mmol/L)	0.8±0.1	0.8±0.1	0.6±0.1
HDL (mmol/L)	1.0±0.02	1.1 ±0.1	1.0 ±0.1
LDL (mmol/L)	1.4 ±0.1	1.1±0.05	1.2 ±0.1

*CHOL= Cholesterol; TRIG = Triglyceride; HDL = High density lipoprotein. Data are expressed as Mean ± SEM of the changes in Cholesterol, Triglyceride, and High density lipoprotein levels. Data were considered statistically significant at P=.05. *- Significant*

The therapeutic effects showed progressive decrease in cholesterol from baseline while triglyceride, HDL, LDL indicates mild fluctuations as shown in Table 3. Differences has been observed in the Cholesterol level of healthy population as well as in patients who have tuberculosis infection in the same locality as patients with tuberculosis generally have lower cholesterol, triglyceride, HDL, and LDL levels which generally increase following anti-tuberculosis chemotherapy. Though the mean values obtained were within reference ranges, there was rather mild decrease in the levels of the entire lipid parameters even though only cholesterol and LDL showed significant decrease compared to the pre-therapy (baseline) levels. It is my opinion that the time frame of eight weeks is a significant limitation in making far reaching scientific declarations. However, the decrease in lipid profile could be part of the pathophysiological mechanism of the tuberculosis infections that is still ongoing during the period. Thus, there are suggestive grounds for the recommendations of lipid supplementation such as egg, omega-3 and fish oil, in patients taking the anti-tuberculosis drugs [22].

4. CONCLUSION

The present study showed some adverse effect of anti-tuberculosis therapy on humans as demonstrated by significant changes in some of the biochemical parameters. The changes though statistically significant where within the normal reference ranges and not severe enough to warrant discontinuation of therapy during the intensive phase of anti-tuberculosis therapy.

CONSENT

All patients that took part in this study were adequately informed and filled the consent form before participating as subject in this study.

ETHICAL APPROVAL

Ethical approval was secured from the concerned health facility.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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