Effect of Artemisinin Based Combination Therapy on the Liver and Kidney of Patient Attending University Health Centre

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ABSTRACT

African countries due to resistance to conventional antimalarial drugs adopted use of artemisinin-based combination therapy (ACTs). This study aimed at evaluating the effect of ACTs on liver and renal functions. Upon approval, patients attending the University Health Centre for treatment of uncomplicated malaria after receiving prescription for ACTs were recruited for the study following their consent. A 3ml blood was collected from the participants immediately after recruitment (Day 0) and seven days later. The participants started ACTs on the day of recruitment. The blood was analysed in the laboratory for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and creatinine respectively. The data obtained at day 0 and 7 were compared by using descriptive analysis such as mean and standard deviation; t-test was used for statistical analysis and significance was considered at $p \leq 0.05$. Seventy-four (74) patients participated including twenty-six (26) males and forty-eight (48) females with mean age of 37.56±13.96years and mean body mass index (BMI) of 25.92±2.99kg/m^2. ALT was elevated in participants from 6.66±5.27IU/L to 6.71±5.48IU/L while creatinine clearance of male participants reduced from 139.10±69.11mL/min to134.25±23.87mL/min. The study showed that ACTs were associated with elevated ALT in participants and reduced renal function in males.

Key words: Artemisinin-based Combination Therapy, Alanine aminotransferase, creatinine clearance, Malaria

INTRODUCTION

Malaria is caused by protozoan known as Plasmodium which is transported by Anopheles mosquito. Plasmodium is classified into five different species which are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi* (Beales and Gilles, 2002; Autino *et al*., 2012). Malaria is a disease assumed to have originated in Africa and spread to other places such as India, Southeast Asia and Mediterranean shore. It is very profound in tropical regions of the world such as sub-Sahara Africa, China, India, South and Central America (Cheesbrough, 2006). The endemicity of malaria in Africa and other regions are determined by either the proportion of individuals in a population with spleenomegaly, or population with laboratory confirmed parasites or number of infective bites per person and number of microscopically confirmed malaria cases detected in a year per unit population (Autino *et al*., 2012). There were 214 million reported cases of malaria globally in 2015, of which eighty-eight percent occurred in Africa, ten percent in South East Asia and two percent in Eastern Mediterranean region. There were 438,000 deaths due to malaria in 2015, ninety percent of death occurred in Africa, seven and two percent occurred in South-East Asia and Mediterranean respectively (WHO, 2015a).

World Health Organisation had recommended that suspected malaria infection should be confirmed by diagnostic testing through either microscopy or rapid diagnostic test before initiation of Artemisinin derivatives combination therapy (ACTs) (WHO, 2015b). This will ensure accurate diagnosis and appropriate treatment that will take care of malaria infection (WHO, 2016). ACTs were recommended for the treatment of uncomplicated malaria infection which had been observed to reduce mortality rate in susceptible children (Thwing, 2011). The approved ACTs which are in circulation in the region are artesunate + amodiaquine, dihydroartemisinin + piperaquine, artesunate + mefloquine, artemether + lumefantrine and artesunate + sulfadoxine-pyrimethamine (Kremsner and Krishna, 2004).

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The African region, most especially Nigeria has a much weakened healthcare system with inadequate facilities and personnel to provide commensurate healthcare services for the population (WHO, 2015a). As a result, facilities to monitor efficacy and adverse effects of ACTs are lacking in our healthcare facilities. Though, there are numerous claims of efficacy of ACTs but documented reports of their adverse effects are lacking. Only one study reported an irreversible hearing loss and another transient elevation of lever enzymes (Toovey and Jamieson, 2004; Price *et al*., 1999). The aim of the study was to evaluate the effects of ACTs on liver and kidney functions.

METHODOLOGY

Materials used for the study: Randox® kits for aspartate aminotransferase, alanine aminotransferase and creatinine, plain bottles for blood collection, 5ml needles and syringes, container rack, weighing balance, meter rule, Unispec 23D Spectrophotometer (UNISCOPE) made by Surgifriend Medicals, England, incubator and refrigerator.

Study setting: The study was conducted among the ambulatory patients with uncomplicated malaria attending the University Health Centre for treatment. Ethical approval was granted by the University Health Centre to conduct the study in the Centre.

Study location: The study was done in University of Uyo, Uyo, Akwa Ibom State. This site is located in the tropical rain forest known to be malaria endemic zone in Nigeria.

Inclusion criteria: Ambulatory patients with uncomplicated malaria and had received prescription for ACTs

Exclusion criteria: Severe malaria cases, diabetic and hypertensive patients were exempted. Patients with long term medication and critically ill patients were excluded.

Study population: A total number of seventy-four (74) participants diagnosed with uncomplicated malaria including males and females who had received prescription for ACTs were recruited in the first phase of the study after their consent was made. They were given questionnaires to fill and the filled questionnaires were returned to the Principal Investigator. A 3ml blood was collected from each of the participants in the first and second phases of the study. Fifty-one (51) participants were followed up in the second phase of the study after seven days of ACTs treatment.

Data collection: The participants were given questionnaires to fill and filled questionnaires were returned to the Principal Investigator. A 3ml blood sample was collected from the recruited participant on the first day of recruitment before the prescribed ACT was consumed and another 3ml blood sample was collected from the participants seven days after the prescribed ACT was consumed. The blood samples collected from the participants were stored in plain bottles and conveyed to the laboratory. The blood samples were centrifuged for 15minutes to obtain serum. The sera were used to evaluate ALT, AST and creatinine by using Randox kits for ALT, AST and creatinine respectively. Standard procedures described in previous publication were used for evaluating the three biochemical parameters (Ajulo *et al*., 2014). Creatinine clearance was calculated from serum creatinine by using Corkcrost-Gault equation as follows (Cockcroft and Gault, 1976):

Creatinine clearance for male =

$$\frac{140 - \text{Age (year)} \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Creatinine clearance for female =

$$\frac{140 - \text{Age (year)} \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

Data analysis plan: Data were analysed by using SPSS version 21 software package. Descriptive statistics were used in the result presentation. Test statistics used was t-test. Level of significance was considered at $p \leq 0.05$.

RESULTS

There were seventy-four (74) participants consisting of twenty-six (26) males and forty-eight (48) females who participated in the first phase of the study after recruitment. Thirteen (13) males and thirty-eight (38) females were followed up after seven days post ACTs consumption. The mean age and BMI of the recruited participants before consumption of ACTs were 37.56±13.96 years and 25.92±2.99 kg/m^2 respectively. The mean age and BMI of those who were followed up after seven days post consumption of ACTs were 38.68±14.25 years and 25.98±2.88 kg/m^2 respectively (Table 1).

Table 1: Demographic parameters

Parameters	General recruitment participants	Followed-up participants
	Frequency (%)	Frequency (%)
Male	26 (35%)	13 (25.5%)
Female	48 (65%)	38 (74.5%)
Total	74	51
	Mean ±SD	Mean ±SD
Age (years)	37.56±13.96	38.68±14.25
Weight (kg)	66.55±6.42	65.62±6.13
Height (m)	1.60±0.06	1.59±0.06
BMI (kg/m^2)	25.92±2.99	25.98±2.88

The result of biochemical parameters of liver function test showed that the participants prior to receiving ACTs had normal liver enzymes ALT (6.66±5.27 IU/L) which was slightly elevated (6.71±5.48 IU/L) seven days after consumption of ACTs. Both liver enzymes AST were elevated prior to consumption of ACTs and seven days after consumption of ACTs. Liver enzyme AST was reduced seven days after consumption of ACTs (Table 2).

The results of kidney function test showed that both male serum creatinine and creatinine clearance of the participants were reduced from 0.74±0.23 mg/dL to 0.69±0.12 mg/dL and from 139.10±69.11mL/min to 134.25±23.87mL/min respectively. The female serum creatinine was reduced from 0.68±0.16mg/dL to 0.65±0.14mg/dL while creatinine clearance increased from 123.0±45.06mL/min to 124.74±27.34mL/min respectively (Table 3).

Table 2: Biochemical parameters of liver function

Phases	Liver function test	
	ALT (IU/L)	AST (IU/L)
First phase (Day 0)	6.66±5.27	14.30±6.31
Second phase (Day 7)	6.71±5.48	13.30±6.59
p-value	0.980	0.452

Table 3: Biochemical parameters of kidney function

Phases	Kidney function test					
	Male		Female		Total	
	Serum creatinine mg/mL	Creatinine clearance mL/min	Serum creatinine mg/mL	Creatinine clearance mL/min	Serum creatinine mg/mL	Creatinine clearance mL/min
First	0.74±0.23	139.10±69.11	0.68±0.16	123.0±45.06	0.69±0.20	127.00±51.96
Second	0.69±0.12	134.25±23.87	0.65±0.14	124.74±27.34	0.66±0.13	127.17±26.60
p-value	0.518	0.812	0.352	0.831	0.429	0.980

DISCUSSION

Malaria is endemic in sub Saharan African region and artemisinin based combination therapy is the widely used regimen for treatment. In this study, evaluation of renal and liver functions after consumption of ACT regimens was done four days after completion of the last dose of ACT regimens. The evaluation was delayed to allow three days of natural recovery course for the liver and renal system before monitoring for the effect of ACT regimens on the renal and liver functions.

The liver enzyme, ALT of participants was found slightly elevated after the recovery period indicating that ACT regimens caused mild injury on hepatic cells but they quickly recover since the period of medication are just three days. There were few studies in support of this claim which indicated that artemisinin derivatives were associated with mild

elevation of serum ALT which often resolved as the therapy continued (Orrell, 2001; Taylor and White, 2004). National Institute of Health (NIH) had confirmed increasing number of reports of idiosyncratic acute liver injury in patients taking artemisinin derivatives (NIH, 2018). In 2016, Adjei reported that liver enzyme, ALT was still elevated at day 7 in about 12% of study participants in a study conducted in four African countries with dihydroartemisinin in combination with piperaquine (Adjei *et al*., 2016).

The creatinine clearance for the male participants reduced after the recovery period indicating that ACT regimens were associated with renotoxicity in male participants. The creatinine clearance for the female participants was slightly increased after the recovery period indicating normal renal function indicating an improved renal function. There has been no other report on effect of artemisinin derivatives combination therapy on human renal function while only animal study indicated preservation of renal antioxidants but multiple doses could lead to renal oxidative stress (Otuechere *et al*., 2012). In this study we could not identify the reason for discrepancy in the renal function of male and female participants after use of ACTs.

In conclusion, the study had indicated that artemisinin based combination therapy had effect on human liver and renal functions.

Recommendation: It is hereby recommended that artemisinin based combination therapy should not be used without prescription and above the therapeutic dose range. More studies are required on effect of long-term use of artemisinin based combination therapy especially on renal function in a larger population.

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REFERENCES

Adjei A, Narh-Bana S, Amu A, Kukula V, Nagai RA, Owusu-Agyei S, Oduro A *et al.*, (2016). Treatment outcomes in a safety observational study of dihydroartemisinin/piperaquine (Eurartesim®) in the treatment of uncomplicated malaria at public health facilities in four African countries. *Malaria Journal*, 15:43.

Ajulo MO, Omole MK, Moody JO (2014). Impact of Highly Active Antiretroviral Therapy (HAART) on organs of HIV-infected Children in Abia State, Nigeria. *British Journal of Pharmaceutical Research*, 4(7): 837-848.

Autino B, Noris A, Russo R and Castelli F (2012). Epidemiology of Malaria in Endemic Areas. *Mediterranean Journal of Hematology and Infectious Diseases*, 4(1): e2012060, DOI 10.4084/MJHID.2012.060

Beales PF and Gillies HM (2002). *Rationale and technique of malaria control. In:Warrell Da, Gilles HM, editors. Essential malariology. 4th Edition*, Arnold; London, *pp107-190.*

Cheesbrough (2006). *District laboratory practice in tropical countries*. New York, *Cambridge press*. Part 1, 2nd edition; 249-258.

Cockcroft DW and Gault MH (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, 16(1):31-41.

Kremsner PG, and Krishna S (2004). Antimalarial combinations. *Lancet*, 364:285–294.

National Institute of Health (2018). Artemisinin Derivatives: Clinical and research information on drug induced liver injury. www.livertox.nih.gov/artemisininderivatives. accessed on February 25.

Orrell C, Taylor WR, Olliaro P (2001). Acute asymptomatic hepatitis in a healthy normal volunteer exposed to 2 oral doses of amodiaquine and artesunate. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 95: 517-518.

Otuechere CA, Edewor G, Kale OE, Ekor M (2012). Subacute therapeutic dosing of Artemisinin-Lumefantrine and Artesunate-Amodiaquine combination preserved plasma cholesterol, renal antioxidants status and organ weight in rats. Malaria research and treatment. *Article ID* 257986.

Price R, van Vugt M, Phaipun L, Luxemburger C, Simpson J, Mcgready R, Ter Kuile F, Kham A, Chongsuphajaisiddhi T, White NJ, and Nosten FO (1999). Adverse effects in patients with acute falciparum malaria treated with artemisinin

derivatives. *American Journal of Tropical Medicine and Hygiene*, 60(4): 547–555.

Taylor WR, White NJ (2004). Antimalarial drug toxicity: a review. *Drug Safety*, 27: 25-61

Thwing J, Eisele TP, Steketee RW (2011). Protective efficacy of malaria case management and intermittent preventive treatment for preventing malaria mortality in children: a systematic review for the Lives Saved Tool. *BMC Public Health*; 11:S14 (http:// www.ncbi.nlm.nih.gov/pubmed/21501431, (Accessed November 19, 2017).

Toovey S, and Jamieson A (2004). Audiometric changes associated with the treatment of uncomplicated falciparum malaria with co-artemether. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 98**:**261–267.

WHO (2015a). World malaria report.www.who.int/malaria (Accessed January 20, 2018)

WHO (2015b). Guideline for the treatment of malaria, Third Edition. www.who.int/malaria/publication (Accessed January 27, 2018)

WHO (2016). World Malaria Report. Geneva: World Health Organization. www.who.int (Accessed February 1, 2018).