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Research Article

LONG TERM EFFECT OF ARTEMISININ COMBINATION THERAPIES (ACTS) ON THE KIDNEY FUNCTION AND ELECTROLYTE BALANCE IN HEALTHY MALE WISTAR RATS

[*]A. U. Ijeomah[1], M. N. Ugwu[2] and K. Dasofunjo[2]
[1]*Department of Biochemistry and Molecular Biology, Faculty of Natural and Applied Sciences, Nasarawa State University, Keffi, Nigeria*
[2]*Department of Medical Biochemistry, Faculty of Basic Medical Sciences, Cross River University of Technology, Okuku Campus*
**Author for Correspondence: ugwumelvin@crutech.edu.ng*

ABSTRACT
The current practice in treating the cases of malaria is based on the concept of combination therapy. Today the production, prescription and application of ACT in the treatment of uncomplicated malaria cases have significantly increased. In this study the effect long term oral administration of artesunate-amodiaquine and arthemeter-lumefantrine at different doses on kidney function and electrolyte balance were investigated in healthy male albino rats. Thirty five albino rats were divided into seven groups. Group 1 (control) received distilled water, Group 2 received 1.43mg/3.86mg/kg body weight of AA, Group 3 received 2.8mg/7.7mg/kg body weight of AA, Group 4 received 5.71mg/15.14mg/kg body weight of AA, Group 5 received 0.57mg/3.43mg/Kg body weight of AL, Group 6 received 1.14mg/6.86mg/Kg body weight of AL and Group 7 received 2.28mg/13.72mg/Kg body weight of AL. The different doses of the drug were administered once daily for 18 days after and the serum creatinine, urea, blood urea nitrogen (BUN), sodium, potassium, chloride and bicarbonate were determined. Serum urea, creatinine and BUN increased significantly ($p<0.05$) compared to control. There were significant increase in the level of Na^+, K^+, Cl^- and HCO_3^- in serum ($p>0.05$) compared to control. The results from the biochemical analyses indicate that the integrity of the kidney might have been affected by prolonged administration of the drugs.

Key Words: *Malaria, Urea, Creatinine, BUN and Electrolytes*

INTRODUCTION
Malaria is a mosquito-borne infectious disease of the blood caused by the parasite, *Plasmodium sp*. It spreads through the bite of infected female *Anopheles* mosquito and is endemic in tropical and sub-tropical regions including parts of America, Asia and Africa (Onyesom, 2012). Malaria is presently endemic in a broad band around the Equator, in areas of the Americas, many parts of Asia, and much of Africa. It is in sub-Saharan Africa where 85 – 90% of malarial fatalities occur (Onyesom and Onyemakonor, 2011). In Africa, malaria is present in both rural and urban areas, though the risk is lower in larger cities (Keiser *et al.,* 2004).
Artemisinin is a natural component of the plant *Artemisia annua*, concoctions of which have been used for a very long time in traditional Chinese medicine for the treatment of fever (Etim *et al.,* 2016). In 1972, the component responsible for the pharmacodynamic action, *qinghaosu* or artemisinin, has been isolated from the leaves of this plant, and its activity against the malaria parasite *Plasmodium falciparum* was subsequently demonstrated. A number of semi-synthetic derivatives were also prepared for use in malaria combat programmes. Their properties and therapeutic usefulness have been repeatedly reviewed (Olliaro and Taylor, 2003; Sriram *et al.,* 2004, Olayemi *et al.,* 2012). Best known among the different derivatives are artemether, arteether (artemotil), artesunate and artenimol (β-dihydroartemisinin, DHA). The biological activity of artemisinin and its derivatives is based on the reactivity of the endoperoxide bridge, the common structural feature of artemisinin and all of its derivatives (Frey *et al.,* 2010; Etim *et al.,* 2016).

Many drugs are available for the treatment of uncomplicated malaria (Ewenighi, 2013). However, control in areas where malaria is endemic is limited by drug resistance, the toxic effects of some agents, and the relatively high cost and limited availability of newer drugs (Mankwe *et al.*, 2016, Etim *et al.*, 2016). This study was designed to assess the toxicity of artesunate-amodiaquine and artemether-lumefantrine on kidney function when taken for long time as often the case in some rural areas on Nigeria.

MATERIALS AND METHODS

Drugs

The study was conducted using ACTs; artesunate/amodiaquine 100/270mg (Winthrop) and artemether/lumefantrine 20/120mg (Coartem® novatis) which was purchase from Benjonason Pharmacy Keffi, Nasarawa State, Nigeria. All manufactured by Novertis Pharmaceuticals Corporation Suffern, New York, USA. Drugs were administered in distilled water obtained from the Department of Biochemistry and Molecular Biology, Faculty of Natural and Applied Sciences, Nasarawa State University, Keffi, Nigeria.

Animals

Thirty five **(**35) healthy male albino rats of weight in the range of (50-100g) were obtained from National Veterinary Research Institute (NVRI), Vom, Jos, Plateau State, Nigeria were used for the study. All the animals were housed in metallic cages and well ventilated room provided with 12:12hours of light and dark cycle daily at approximately 25^{o}C. They were fed with vital feeds and tap water *ad libitum*. After the two weeks of acclimatization, the rats were weighed and divided into 7 groups with 5 per group. The animals in group 2, 3 and 4 were given varying doses (1.43mg/3.86mg/kg, 2.86mg/7.71mg/kg and 5.72mg/15.42mg/Kg body weight of artesunate/amodiaquine while group 5, 6 and 7 were given0.57mg/3.43mg/Kg, 1.14mg/6.86mg/Kg and 2.28mg/13.72mg/Kg body weight of Artemether/lumefantrine (AL) respectively of the drugs dissolved in distilled water per body weight for 18 days. Animals in group 1 served as the negative control. The negative control received distilled water and feed. All the animals were subjected to overnight fasting before sacrifice. The principles governing the use of laboratory animals as laid out by the Department of Biochemistry and Molecular Biology, Nasarawa State University, Keffi were dully observed.

Collection of blood sample

At the end of the experiment the animals were sacrificed under chloroform anaesthesia. Blood samples were removed through cardiac puncture into a plane sample bottle. Sera were gotten from the blood by centrifugation and were used for biochemical investigations.

Biochemical assays

The separated serum were use to analyze for various biochemical parameters such as; urea, creatinine, sodium, potassium, chloride and bicarbonate.

Determination of urea concentration

Serum urea concentration was estimated based on the method of Tobacco *et al.* (1979).

Determination of serum creatinine concentration

Serum creatinine concentration was carried out according to the method of Allen (1982).

Determination of Serum Chloride

Determination of serum chloride using titrimetric method as described by Clark *et al.*, (1942).

Determination of Serum Sodium

Determination of sodium by colorimetric method as described by Stone and Goldzieher, (1942)

Determination of Serum Bicarbonate

Determination of bicarbonate by enzymatic method as described by Forrester *et al.*, (1976).

Determination of potassium

Determination of potassium by colorimetric method as described by Ng *et al.*, (1992).

Statistical Analysis

Statistical differences between the mean was analyzed by ANOVA. Resulting data were represented as mean standard deviation.

RESULTS

Table 1: Effect of oral administration of Artesunate amodiaquine (AA) and arthemeter lumefetrine(AL) for 18 days on serum creatinine, urea, and blood urea nitrogen of Wistar albino rat.

GROUP	UREA (mg/dl)	CREAT (mg/dl)	BUN (mg/dl)	BUN/CREAT
CONTROL	38.45±2.15^{a}	0.50±0.02^{a}	17.93±1.01^{a}	35.68±3.31^{a}
1.43mg/3.86mg AA	42.76±3.89^{ab}	0.53±0.02^{b}	19.55±1.07^{b}	36.69±2.93^{a}
2.86mg/7.7mg AA	44.10±3.42^{b}	0.55±0.02^{b}	19.92±0.22^{b}	36.24±1.39^{a}
5.72mg/15.42mg AA	45.22±3.93^{b}	0.56±0.03^{b}	20.26±0.62^{b}	36.11±1.35^{a}
0.57mg3.43mg AL	42.45±4.29^{ab}	0.54±0.01^{b}	19.66±0.69^{b}	36.17±1.74^{a}
1.14mg6.86mg AL	44.98±4.87^{b}	0.55±0.02^{b}	19.79±1.01^{b}	36.23±1.38^{a}
2.28mg/13.17mg AL	45.85±3.56^{b}	0.56±0.01^{b}	20.16±0.58^{b}	36.01±1.15^{a}

Values were expressed as Mean ± SD of replicate determinations. Value bearing super script a, b are statistically significant along the same column when compared with the control at (P < 0.05).

In the table above, there was a significant (P<0.05) increase in serum urea, creatinine and BUN in all treated groups when compared to the control. There was no significant difference (P<0.05) in BUN/creatinine ratio when compared to the control. Though there was a marginal increase in all treated groups when compared to control.

Table 2: Effect of oral administration of Artesunate Amodiaquine (AA) and arthemeter lumefetrine(AL) for 18 days on serum sodium, potassium, chloride and bicarbonate of Wistar albino rat.

GROUP	Na^{+} (mmol/l)	K^{+}(mmol/l)	Cl^{-} (mmol/l)	HCO_3^{-}(mmol/l)
CONTROL	131.00±5.79^{a}	5.47±0.38^{a}	66.40±4.93^{a}	35.80±6.18^{a}
1.43mg/3.86mg AA	132.40±4.93^{ab}	6.49±0.40^{b}	74.60±5.03^{abc}	41.95±7.77^{ab}
2.86mg/7.7mg AA	138.20±4.97^{bc}	6.94±0.57^{bc}	81.06±7.16^{bc}	42.82±6.01^{ab}
5.72mg/15.42mg AA	140.00±4.47^{c}	7.24±0.41^{c}	82.69±7.63^{c}	45.66±5.85^{b}
0.57mg/3.43mg AL	133.80±4.38^{abc}	6.40±0.56^{b}	72.30±4.59^{ab}	42.76±7.64^{ab}
1.14mg/6.86mg AL	137.60±5.55^{abc}	6.85±0.45^{bc}	77.14±6.40^{bc}	43.62±5.44^{ab}
2.28mg/13.17mg AL	139.60±1.67^{c}	6.86±0.56^{bc}	79.73±7.34^{bc}	45.31±4.65^{b}

Values were expressed as Mean ± SD of replicate determinations, value bearing super script a, b, c are statistically significant along the same column when compared with the control at (P < 0.05)

In the table above, there was a significant (P<0.05) increase in serum sodium, potassium, chloride and bicarbonate in all treated groups when compared to the control.

DISCUSSION

Malaria is one of the most important infectious diseases worldwide. In Africa, which bears the greatest burden of this disease, controlling efforts have been largely unsuccessful. New therapies are urgently

needed and it is generally agreed that an artemisinin-based combination therapy (ACT) offers the best opportunity for effective treatment and prevention of drug-resistant parasites (Miller and Su, 2011; Charles *et al.,* 2013). Artemisinin derivative-based combination therapy (ACT) has been advocated as the therapy of choice to handle widespread drug resistance in *Plasmodium falciparum* malaria, at the same time preventing recrudescence that usually occurs with artemisinin monotherapy (Nguyen *et al.,* 1996; Olurishe *et al.,* 2007). ACTs are preferred because artemisinin compounds have rapid parasite and fever clearance effects and also reduce gametocyte rate with the potential to reduce transmission (Meremikwu, 2006). In malaria endemic regions, malaria infection may occur repeatedly in individuals within months which warrant the use of repeated doses of antimalarials. This situation occurs more prominently in individuals with increased susceptibility such as children, pregnant women and immunocompromised patients (Diagne *et al.,* 2000; Tiono *et al.,* 2013; Iribhogbe *et al.,* 2017) and this action might result to drug toxicity.

The kidney removes waste produced by metabolism, this includes the nitrogenous waste urea, from protein catabolism and uric acid, from nucleic acid metabolism and excess water (fluid) in the blood, as it flows through the body. In this study, effects of orally administration of artemisinin based combination therapies on kidney function were investigated. Kidney function tests are required either to demonstrate the presence or absence of active lesion in kidney, or to assess the normal functioning capacity of nephron (Yakubu *et al.,* 2006).

Urea is a by-product of protein metabolism by the liver, and is therefore removed from the blood by the kidneys. Urea freely filters through the glomerulous, but is reabsorbed by the renal tubules in a flow-dependent fashion. The higher the flow rate, the greater amount of urea nitrogen is cleared from circulation and eliminated through the kidneys (Gaspari *et al.,* 1998; Waiker and Bonventre, 2008). As a result, the level of circulating urea nitrogen, along with serum creatinine, serves as a primary measure of kidney function. Increase in plasma urea concentration observed in this study could be as result of kidney damage.

Serum creatinine is another metabolic waste product generated from muscle metabolism and freely filtered by the glumerulous, but does not undergo tubular reabsorption. Its steady rate of elimination is frequently used to generate an index or ratio with BUN values for normalized evaluations (Lum and Leal-Khouri, 1989; Nankivell, 2001; Traynor *et al.,* 2006). Creatinine is produced at a constant rate depending on the muscle mass of the body. Increase in serum creatinine usually, is as a result of impaired kidney function which reduces the excretion of creatinine resulting to increased blood creatinine. It could also increase as a result of dehydration. Increase in creatinine observed in the groups treated with drugs could be as a result of damage to the kidney. Also increase in blood urea nitrogen (BUN) in animals treated with AL and AA may be due to kidney problems or urinary tract problem.

Elevation of urea and creatinine levels is an indication of renal dysfunction (Mouton and Holder, 2006; Traynor *et al*., 2006; Etim *et al.,* 2014). This indicates that prolong treatment of artesunate-amodiaquine and arthemeter-lumefetrine may affect kidney function in the rats. An elevation in these parameters in this study is highly suggestive of renal toxicity (Perrone *et al.,* 1992; Nankivell, 2001; Traynor *et al.,* 2006; Etim *et al.,* 2016**).** The observed toxicity is believed to involve the formation of an electrophilic metabolite, which can bind to cellular macromolecules and initiate hypersensitivity reactions (Al-Kadi, 2004). The long term administration of the drugs might have either interfered with creatinine metabolism leading to increased synthesis or the tissue might have compromised all or part of its functional capacity of tubular excretion (Mitchell *et al.,* 1972; Zilva *et al.,* 1991; Yakubu *et al.,* 2006).

Electrolytes are minerals present in blood and other body fluids in form of dissolved salt. There optimum range is essential for proper physiological activities (Rani *et al.,* 2015). Inorganic electrolytes occur in large quantities in cellular fluids and can dissociate readily into their constituent ions or radicals in the extracellular and intracellular compartments (Zilva, 1991). Sodium (Na) is known as the major cation of exracellular fluid. It regulates the normal distribution of water and osmotic pressure in various body fluids. Various health problems occur due to Na^+ ion disturbance (Andersen *et al.,* 1996; Day *et al.,*

2005). Potassium (K) is identified as a crucial electrolyte for accurate functioning of all body cells, tissues and organs. It maintains blood pH and water levels in the body. It is particularly important in skeletal and smooth muscle contraction (Maitland *et al.*, 2005).

Medications can interfere with the absorption of electrolytes, alter hormonal responses affecting homeostasis and directly impact organ function responsible for maintaining electrolyte balance (Buckley, 2012). It has been observed that cellular membrane electrolyte transporter Na^+-K^+-ATPase (Shahid *et al.*, 2005) and the functions of Ca^{2+}-Mg^{2+}-ATPase, Na^+/Ca^{2+} exchanger, and Ca^{2+} pump, which are located in the cell membrane, mitochondria or endoplasmic reticulum, have been shown to be impaired in some diseases in which certain organs were damaged (Mikaelian *et al.*, 2013).

Increased level of sodium in AA and AL administered to rats is an indication of alteration in important biochemical parameters, such as an increase production of aldosterone and other mineral corticoids which will in turn increase the tubular reabsorption of Na^+ or decrease production of either antidiuretic hormone or decreased tubular sensitivity to the hormone (Tietz *et al.*, 1994). Hypernatraemia could in a way serve as an indicator of liver disease (Zilva, 1991). Potassium ion plays an important role during transmission of nerve impulses along the nerve cells to receptor cells. Sodium pump maintains the intracellular K^+ concentration. As sodium is absorbed, potassium is secreted and vice versa (Horton *et al.*, 1993).

Increased serum chloride is associated with hyperchloremia. Chloride is an electrolyte and works to ensure that the body's metabolism is working correctly. The kidney controls the level of chloride in the body. Therefore, when there is disturbance in the body's chloride it is related to the kidney. Increase in bicarbonate in animals administered with AA and AL may be attributed to metabolic alkalosis as a result of loss of hydrogen ion and these occurs when the distal delivery of sodium increases in the presence of aldosterone, which stimulates the electrogenic epithelial sodium channel on the collecting duct. As the channel reabsorbs sodium ion the tubular lumen becomes negatively charged leading to secretion of hydrogen in to the lumen and as these happens bicarbonate in gained on the extracellular space. This increase could also be as a result of inadequate ventilation which results to accumulation of CO_2 (Francis and Cox, 2010).

Drug-induced nephrotoxicity is a common complication of several medications and diagnostic agents. Manifestations of drug-induced nephrotoxicity include acid–base abnormalities, electrolyte imbalances, urine sediment abnormalities, proteinuria, pyuria, hematuria, and, most commonly, a decline in the glomerular filtration rate (Nolin and Himmerlfarb, 2009). This study indicates that prolong treatment of artesunate-amodiaquine and Arthemeter-lumefetrine may affect kidney function in the rats. Though the nephrotoxicity might be due the partner drugs not the artemisin derivatives. Therefore further research is needed to clarify this issue.

CONCLUSION

Results of the present investigation have shown that artemisinin based combination therapy is capable of producing alteration in some biochemical parameters. The drugs have undergone biotransformation in the liver cells which gives rise to free radical that might subsequently unleash damage to cellular macromolecules such as enzymes, membranes, and genetic material.

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