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KIDNEY FUNCTIONS IN WISTER RATS TREATED WTH ARTESUNATE AND AMODIAQUINE

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ABSTRACT: Malaria is a mosquito bone disease caused by plasmodium parasite. Several drugs have been developed and used in treatment of this disease but, many of these medications results in adverse side effects. This study evaluates the effects of artesunate and amodiaquine (antimalaria agents) in renal functions of wister rats. Fifteen wister rats were divided into 3groups (n=5). Group 1 served as normal control, groups 2 and 3 were treated with 8mg/kg artesunate and 30mg/kg amodiaquine respectively for 5 days after which blood samples were collected and centrifuged to obtain serum. Blood urea nitrogen (BUN) and Creatinine (CRT) levels were determined using randox kits. Kidney histology was done using haematoxylin-eosin stain. Results were analyzed using one way ANOVA with statistical significance taken at $p<0.05$. BUN increased significantly in 30mg/kg amodiaquine treated rats when compared with normal control and 8mg/kg artesunate treated rats. There was also significant increase in creatinine level in 30mg/kg amodiaquine treated rats when compared with normal control and 8mg/kg artesunate treated rats. Histological sections shows glomeruli distortions in both artesunate and amodiaquine treated rats. Artesunate increased BUN while amodiaquine increased both BUN and CRT which are potentially toxic at high concentrations. Artesunate may therefore be a preferred medication over amodiaquine in malaria treatment because of its reduced side effects on kidney functions.

KEY WORDS: Malaria, artesunate, amodiaquine, medication, renal function

INTRODUCTION:

Malaria is a life threatening infectious disease affecting humans. It is caused by parasitic protozoans belonging to the *Plasmodium species* and transmitted through the bite of female anopheles mosquito (WHO; 2014). This disease is widespread in the tropical and subtropical regionsof the equator (Caraballo *et al*., 2014) which includes the Sub-Saharan Africa, Asia, and America (WHO; 2014). There were 296 million cases of malaria worldwide in 2015 resulting in an estimated deaths of 731,000 (GBD; 2015) with approximately 90% of the mortality in Africa (WHO; 2016). However, the control of malaria-

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requires an integrated approach including prevention and treatment with effective anti-malaria agents. In malaria endemic areas like Nigeria, treatment policies have been updated from the use of monotherapy agents like chloroquine to combination therapies. Artesunate is one of the medications used in treatment of malaria that is well tolerated although it is often used in combination with other medications as first line of treatment against malaria and to reduce the risk of resistance (GBD 2015). It has the highest treatment success, with lower incidence of adverse effects, but despite its beneficial effects, cases of toxicity still exist (WHO; 2016). Similarly, amodiaquine is an antimalaria agent used against *Plasmodium falciparum* with varying side effects (Olliaro *et al*., 2003; Nair *et al*., 2012). It is not usually recommended to prevent malaria and more so, the World Health Organization has expressed contradictory positions on its use against malaria infection because of its adverse reactions. However, other studies suggested that adverse reactions are rare when amodiaquine is administered for treatment (Nevill *et al*, 1994; Radloff *et al*., 1996). The kidney is an important organ that may be exposed to reactions following artesunate and amodiaquine administration in humans. The kidneys usually excrete waste products that may be toxic if allowed to accumulate in the blood and therefore, any damage caused to the kidneys may also impair its functions. Although artesunate and amodiaquine have been reported to have adverse reactions, but, there is paucity of information on their relative effects on kidney functions. This study was therefore designed to evaluate the relative effects of these drugs on kidney functions in wister rats.

MATERIALS AND METHODS:

Experimental design and drug purchase

Fifteen Wister rats weighing (150-200g) were obtained from the Animal House, College of Medicine, University of Medical Sciences, Ondo, Nigeria. They were housed in well aerated cages, maintained on standard rat chow with free access to drinking water according to the guidelines and regulations of the National Institute of Health (1985). Rats were divided into 3 groups of 5 rats per group. Group 1 served as normal control, group 2 and 3 were treated with 8mg/kg artesunate (Papiya *et al*., 2015) and 30mg/kg amodiaquine (White *et al*., 1999) respectively. Artesunate was purcahased from the Adams Pharmaceutical (Annhui) Cooperative, limited, Xuancheng Economic and Technical Development Zone China, while amodiaquine was purchased from Ajanta Pharmaceutical limited, Mumbai, India.

Blood collection and determination of Blood Urea Nitrogen and Creatinine levels

After 5 days of post-treatments with artesunate and amodiaquine in rats, blood samples were collected through cardiac puncture under mild anaesthesia (0.6ml/100g body weight, urethane *i.p*) and thereafter, rats were sacrificed through cervical dislocation. The blood samples were centrifuged at 3000 r.p.m to obtain serum which was carefully taken into another plain tube using Pasteur pipette. Blood urea nitrogen and creatinine levels were quantified using randox kits and their absorbance measured using spectrophotometer (Nada *et al*., 2016). The kidney was excised and stored in 10% formalin and thereafter assessed for possible damages using heamatoxylin-eosin stain (Fieldman *et al*., 2014).

Statistical Analysis

Results obtained were analyzed using one-way analysis of variance (ANOVA) and Neuman's keul post-hoc test. Data were expressed as mean ±SEM with the level of statistical significance taken at $p<0.05$.

RESULTS:

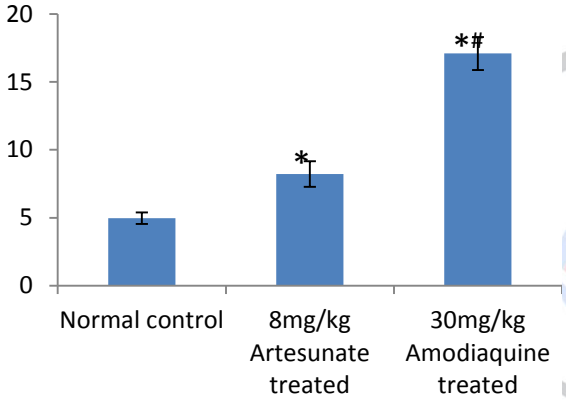


Figure 1: Effects of artesunate and amodiaqiune on Blood Urea Nitrogen level. Data were expressed as Mean ± SEM; P<0.05. * indicate values significantly different from the normal control while # indicate value significantly different from 8mg/kg Artesunate treated (n=5)

Figure 1 shows Blood Urea Nitrogen (BUN) levels in normal control, 8mg/kg Artesunate treated and 30mg/kg Amodiaquine treated rats. There was significant increase ($p<0.05$) in BUN in 8mg/kg Artesunate and 30mg/kg amodiaquine treated rats when compared with normal control. The percentage increases are 39.47% and 70.91% respectively. Blood urea nitrogen significantly increased ($p<0.05$) in 30mg/kg Amodiaquine treated group when compared with 8mg/kg Artesunate treated group with percentage increase of 51.94%.

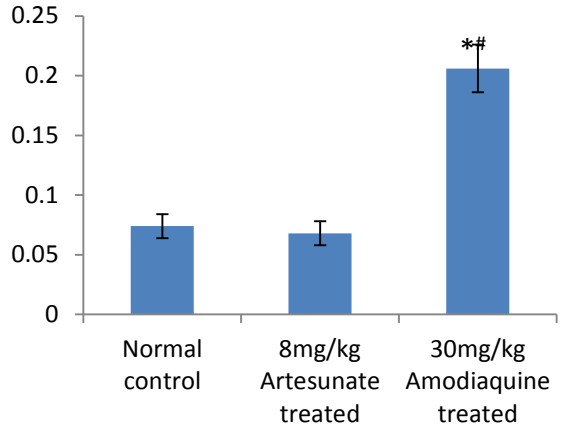


Figure 2: Effects of artesunate and amodiaqiune on Creatinine level. Data were expressed as Mean ± SEM; P<0.05. * indicates value significantly different from the normal control while # indicates value significantly different from 8mg/kg Artesunate treated (n=5)

Figure 2 shows Creatinine levels in normal control, 8mg/kg Artesunate treated and 30mg/kg Amodiaquine treated rats. There was significant increase ($p<0.05$) in creatinine level in 30mg/kg amodiaquine treated rats when compared with normal control and 8mg/kg Artesunate treated group. There percentage increases in creatinine level are 60.23 and 70.14 respectively. However, creatinine level in 8mg/kg Artesunate treated group was not significantly different ($p>0.05$) from normal control.

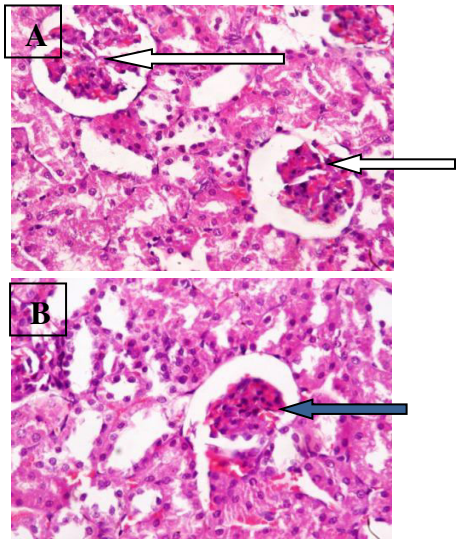
DISCUSSION AND CONCLUSION:

Blood urea nitrogens are nitrogenous waste products of metabolism produced when proteins are broken down to produced ammonia (Price *et al*., 2000). This ammonia undergoes deamination and are converted to urea by liver enzymes (Miltuninovic *et al*., 1975). Blood urea concentration depends on protein intake, ability of the body to catabolize proteins and renal excretion through the kidneys. The increase in urea concentration observed in artesunate and

amodiaquine treated rats may be due to distortion in the glomerulus of the renal tubules and decrease capsular space as shown in the photomicrograph (Plate 1C). The increased in urea concentration suggests a decrease glomerular filtration rate and accumulation of waste products of metabolism that should be excreted in urine.

Creatinines are nitrogenous waste products of metabolism produced endogeneously from breakdown of muscle creatine and can serve as an indicator of renal function (Maroni *et al*., 1985). The increased in creatinine in amodiaquine treated rats also suggest possible distortion of the glomerulus as shown in the photomicrograph (Plate 1C) and reduced glomerular filtration rate (Laterza *et al*., 2002). Studies have shown that creatinine levels are not influence by diet and therefore are good indicators of renal function.

In conclusion, both artesunate and amodiaquine caused glomeruli distortions with amodiaquine exerting the greater effects. Both drugs caused reduced glomerular filteration rate and accumulation of waste products of metabolism that may be potentially toxic if not excreted in urine.



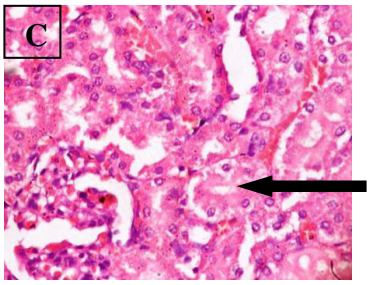


Plate 1 (A – C): Shows sections stained with H & E showing architecture of the Kidney in A (Control), B (8mg/kg Artesunate treated rats) and C (30mg/kg Amodiaquine treated rats). A showed architecture of the kidney with normal glomeruli and capsular spaces (white Arrow), B & C showed architecture of the kidney with distorted glomeruli and inflammatory cells (Blue and Black Arrows respectively) X 400.

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